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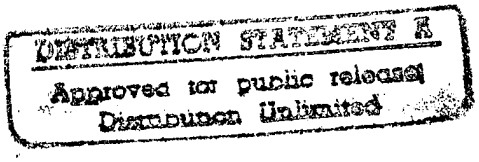
HUMAN RESPONSES TO THERMAL STRESS

By

C. Bruce Wenger, M.D., Ph.D.

April 1996



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The body of a homeotherm may be divided into a core, whose temperature is maintained within narrow limits, regardless of environmental temperature, and a peripheral shell, whose temperature is strongly influenced by the environment. Homeotherms regulate core temperature in order to provide a stable physical-chemical environment for metabolic and other physiological processes. Heat content of the body depends on the balance between metabolic heat production and heat exchange with the environment by convection, radiation, and evaporation which, in humans, is largely evaporation of sweat. Heat exchange by convection and radiation depends on the temperature difference between skin and environmental temperatures, heat exchange by evaporation of sweat depends on the wetness and temperature of the skin and the ambient water vapor pressure, and both convection and evaporation depend on air movement. Animals control heat exchange behaviorally, through the willed, conscious use of any means available; and physiologically, through responses which ordinarily function independently of consciousness. Thermoregulation is the name given to these processes for controlling body heat balance. Physiological means of thermoregulation include control of metabolic heat production, control of skin temperature through skin blood flow, and control of skin wetness through sweating. The physiological control of these responses according to core and skin temperatures, and the effects of various physiological processes--including circadian rhythms, the menstrual cycle, exercise and acclimatization to heat and cold--on the control are discussed. Clothing affects heat by creating a microenvironment between the clothing and the skin. Finally there is a discussion of clinical and pathological issues. This discussion includes the effect of fever on the body's defense mechanisms; the effects of age, sex, drugs and disease states on thermoregulation; and pathological states caused or aggravated by heat or cold stress.

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PREFACE

This technical note is adapted from the author's chapter The regulation of body temperature. In: Medical Physiology. (Chap. 31) R.A. Rhoades and G.A. Tanner (Eds.) Boston, MA: Little, Brown, 587-613, 1995. The principal changes made in preparing this technical note from the chapter are the inclusion of Fig. 4; the addition of material about ionic permeabilities of cell membranes of poikilotherms, clothing, sodium concentrations in sweat of patients with cystic fibrosis, and thermoregulatory effects of sunburn and heat rash; and an update of the list of suggested reading.

INTRODUCTION: IMPORTANCE OF TISSUE TEMPERATURE

Human beings, like other mammals, are homeotherms, or warm-blooded animals, and regulate their internal body temperatures within a narrow range near 37°C (Fig. 1), in spite of wide variations in environmental temperature. Internal body temperatures of poikilotherms or cold-blooded animals, by contrast, are governed by environmental temperature. The range of temperatures that living cells and tissues can tolerate without harm extends from just above freezing to nearly 45°C—far wider than the limits within which homeotherms regulate body temperature. What biological advantage do homeotherms gain by maintaining a stable body temperature? As we shall see, tissue temperature is important for two reasons.

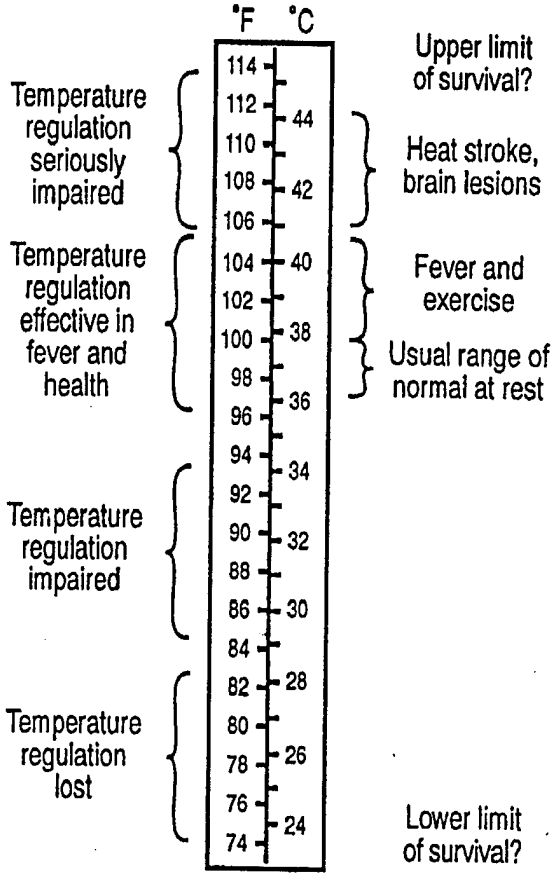

Figure 1. Ranges of rectal temperature found in healthy persons, patients with fever, and persons with impairment or failure of thermoregulation. (Modified from DuBois, E. F. Fever and the Regulation of Body Temperature, Springfield, Ill., Chas. C. Thomas, 1948.)

TEMPERATURE EXTREMES INJURE TISSUE DIRECTLY.

High temperatures alter the configuration of protein molecules, and their overall structure, even though the sequence of amino acids is unchanged. Such alteration of protein structure is called denaturation. A familiar example of denaturation by heat is the coagulation of the albumin in the white of a cooked egg. Since the biological activity of a protein molecule depends on its configuration and charge distribution, denaturation inactivates a cell's proteins, and injures or

kills the cell. Injury occurs at tissue temperatures higher than about 45°C, which is also the point at which heating the skin becomes painful. The severity of the injury depends on both the temperature to which the tissue is heated and how long the heating lasts.

As a water-based solution freezes, ice crystals consisting of pure water form, so that all dissolved substances in the solution are left in the unfrozen liquid. Thus as more ice forms, the remaining liquid becomes more and more concentrated. Freezing damages cells through two mechanisms. First, ice crystals themselves probably damage the cell mechanically. Second, the increase in solute concentration of the cytoplasm as ice forms denatures the proteins by removing their water of hydration, by increasing the ionic strength of the cytoplasm, and by other changes in the physicochemical environment in the cytoplasm.

TEMPERATURE IS A FUNDAMENTAL PHYSICOCHEMICAL VARIABLE, AFFECTING MANY BIOLOGICAL PROCESSES.

Temperature changes profoundly alter biological function both through specific effects on such specialized functions as electrical properties and fluidity of cell membranes, and through a general effect on most chemical reaction rates. In the physiological temperature range, most reaction rates vary approximately as an exponential function of absolute temperature (T); and increasing T by 10°K increases the reaction rate by a factor of 2 to 3. For any particular reaction, the ratio of the rates at two temperatures 10°K apart is called the Q_{10} for that reaction, and the effect of temperature on reaction rate is called the Q_{10} effect. The notion of Q_{10} may be generalized to apply to a group of reactions that have some measurable overall effect (such as O_2 consumption) in common, and are thus thought of as comprising a physiological process. The Q_{10} effect is clinically important in managing patients who have high fevers and are receiving fluid and nutrition intravenously. A commonly-used rule is that a patient's fluid and calorie needs are increased 13% above normal for each 1°C of fever.

The profound effect of temperature on biochemical reaction rates is illustrated by the sluggishness of a reptile that comes out of its burrow in the morning chill, and becomes active only after being warmed by the sun. Homeotherms avoid such a

dependence of metabolic rate on environmental temperature by regulating their internal body temperatures within a narrow range. A drawback of homeothermy is that in most homeotherms, certain vital processes cannot function at low levels of body temperature that poikilotherms tolerate quite easily. Thus, for example, shipwreck victims immersed in cold water die of respiratory or circulatory failure (through disruption of the electrical activity of the brainstem or heart) at body temperatures of about 25°C, even though such a temperature produces no direct tissue injury, and fishes thrive in the same water. Poikilotherms' advantage in tolerating low body temperatures seems to owe to differences in their cell membranes, and in particular to much lower permeabilities to small ions, so that poikilotherms maintain the concentration gradients of these ions across the cell membranes with much less metabolic energy expenditure than homeotherms require. It may be that as falling body temperature depresses the metabolic rate, homeotherms reach a point at which their ion pumps can no longer maintain sufficient ionic gradients across their "leaky" cell membranes to support heart muscle and nerve cell function; but poikilotherms may be protected from such a fate by their less "leaky" membranes.

BODY TEMPERATURES AND HEAT TRANSFER IN THE BODY

THE BODY IS DIVIDED INTO A WARM INTERNAL CORE, AND A COOLER OUTER SHELL.

The temperature of the shell (Fig. 2) is strongly influenced by the environment; thus its temperature is not regulated within narrow limits as internal body temperature is, even though thermoregulatory responses do strongly affect the temperature of the shell, and especially its outermost layer, the skin. The thickness of the shell depends on the environment and the body's need to conserve heat. In a warm environment, the shell may be less than 1 cm thick; but in a subject conserving heat in a cold environment, it may extend several centimeters below the skin. The internal body temperature that is regulated is the temperature of the vital organs inside the head and trunk which, together with a variable amount of other tissue, comprise the warm internal core.

Heat is produced in all tissues of the body, but is lost to the environment only from tissues in contact with the environment, predominantly from skin but to a lesser degree from the respiratory tract also. We therefore need to consider heat transfer within the body, especially heat transfer (1) from major sites of heat production to the rest of the body, and (2) from core to skin. Heat is transported within the body by two means: conduction through the tissues; and convection by the blood, a process in which flowing blood carries heat from warmer tissues to cooler tissues.

Heat flow by conduction varies directly with the thermal conductivity of the tissues, the change in temperature over the distance that the heat travels, and the area (perpendicular to the direction of heat flow) through which the heat flows; and it varies inversely with the distance that the heat must travel. As Table 1 shows, the tissues are rather poor heat conductors.

Heat flow by convection depends on the rate of blood flow and the temperature difference between the tissue and the blood supplying the tissue. Because the capillaries have thin walls and, taken together, a large total surface area, the capillary beds are the sites where heat exchange between tissue and blood is most efficient. Changes in skin blood flow in a cool environment change the thickness of the shell. When skin blood flow is reduced in the cold, the affected skin becomes cooler, and the underlying tissues—which in the cold may include most of the limbs and the more superfi-

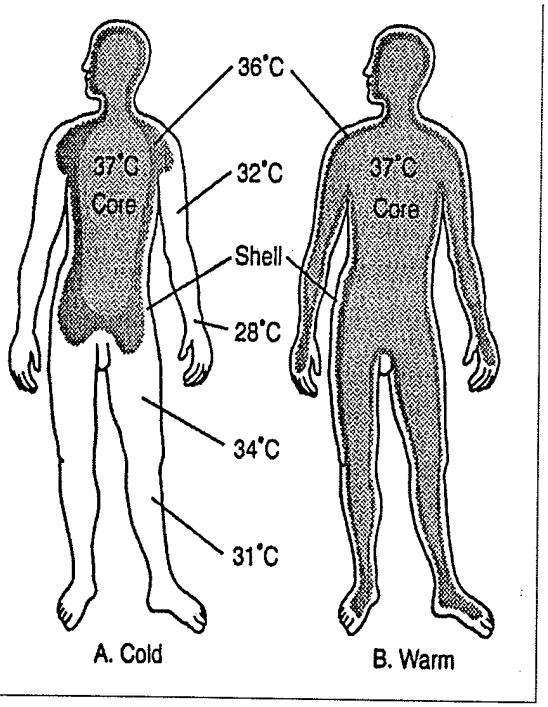

Figure 2. Distribution of temperatures within the body and division of the body into core and shell during exposure to (A) cold and (B) warm environments. The temperatures of the surface and the thickness of the shell depend on the environmental temperature, so that the shell is thicker in the cold and thinner in the heat. (Modified from Elizondo, R.S. Regulation of body temperature. In: Human Physiology (Chap. 28) R.A. Rhoades and R.G. Pflanzer (Eds.) Philadelphia: Saunders, 823-855, 1989.)

Table 1. Thermal conductivities, and rates of heat flow through slabs of different materials 1 m^2 in area and 1 cm thick, with a 1°C temperature difference between the two faces of the slab.

	conductivity	rate of heat flow	
	kcal/(s·m)	kcal/h	Watts
Copper	0.092	33,120	38,474
Epidermis	0.00005	18	21
Dermis	0.00009	32	38
Fat	0.00004	14	17
Muscle	0.00011	40	46
Oak (across grain)	0.00004	14	17
Glass fiber insulation	0.00001	3.6	4.2

cial muscles of the neck and trunk—become cooler as they lose heat by conduction to cool overlying skin and ultimately to the environment. In this way these underlying tissues, which in the heat were part of the body core, now become part of the shell. Thus in addition to the organs within the trunk and head, the core includes a greater or lesser amount of more superficial tissue—mostly skeletal muscle—depending on the body's thermal state.

Since the shell lies between the core and the environment, all heat leaving the body core—except for heat lost through the respiratory tract—must pass through the shell before being given up to the environment. Thus the shell insulates the core from the environment. In a cool subject skin blood flow is low, so that core-to-skin heat transfer is dominated by conduction; the shell is also thicker and thus provides more

insulation to the core, since heat flow by conduction varies inversely with the distance that the heat must travel. Thus changes in skin blood flow, which directly affect core-to-skin heat transfer by convection, also indirectly affect core-to-skin heat transfer by conduction, by changing the thickness of the shell. In a cool subject, the subcutaneous fat layer contributes to the insulation value of the shell both because the fat layer increases the thickness of the shell and because fat has a conductivity about 0.4 times that of dermis or muscle (Table 1), and thus is a correspondingly better insulator. In a warm subject, on the other hand, the shell is relatively thin, and thus provides little insulation. Furthermore a warm subject's skin blood flow is high, so that heat flow from the core to the skin is dominated by convection. In these circumstances the subcutaneous fat layer—which affects conduction but not convection—has little effect on heat flow from core to skin.

CORE TEMPERATURE IS CLOSE TO CENTRAL BLOOD TEMPERATURE.

Core temperature varies slightly from one site to another depending on such local factors as metabolic rate, blood supply, and the temperatures of neighboring tissues. However, temperatures at different places in the core are all close to the temperature of the central blood, and tend to change together. Thus the notion of a single uniform core temperature, though not strictly correct, is a useful approximation. The value of 98.6°F that is often given as the normal level of body temperature may give the misleading impression that body temperature is regulated so precisely that it is not allowed to deviate even a few tenths of a degree. In fact, 98.6°F is simply the Fahrenheit equivalent of 37°C; and, as Fig. 1 indicates, body temperature does vary somewhat. The effects of heavy exercise and fever are quite familiar; and in addition variation among individuals and such factors as time of day (Fig. 3), phase of the menstrual cycle, and acclimatization to heat can cause differences of up to about 1°C in core temperature at rest.

In order to maintain core temperature within a narrow range, the thermoregulatory system needs continuous information about the level of core temperature. Temperature-sensitive neurons and nerve endings in the abdominal viscera, great veins, spinal cord, and especially the brain provide this information. We shall discuss

how the thermoregulatory system processes and responds to this information later in the chapter.

Core temperature should be measured at a site whose temperature is not biased by environmental temperature. Sites used clinically include the rectum, the mouth, and occasionally the axilla. The rectum is well insulated from the environment, so that its temperature is independent of environmental temperature; and it is a few tenths of a degree C warmer than arterial blood and other core sites. The tongue is richly supplied with blood, so that oral temperature under the tongue is usually close to blood temperature (and 0.4 to 0.5°C below rectal temperature); but cooling the face, neck, or mouth can make oral temperature misleadingly low. Tympanic membrane temperature has recently enjoyed a degree of popularity in clinical use because of the ease of measuring it with infra-red sensing devices, and the commercial promotion of such devices. However, the tympanic membrane ordinarily is exposed to ambient air, and most of its blood supply follows a superficial course, since it comes through branches of the external carotid artery. For these reasons tympanic membrane temperature may be seriously biased by ambient temperature, and is unsuitable for evaluating a patient suspected of having a heat illness. If a patient holds his upper arm firmly against his chest so as to close the axilla, axillary temperature will eventually come reasonably close to core temperature. However since this may take 30 minutes or more, axillary temperature is no longer widely used.

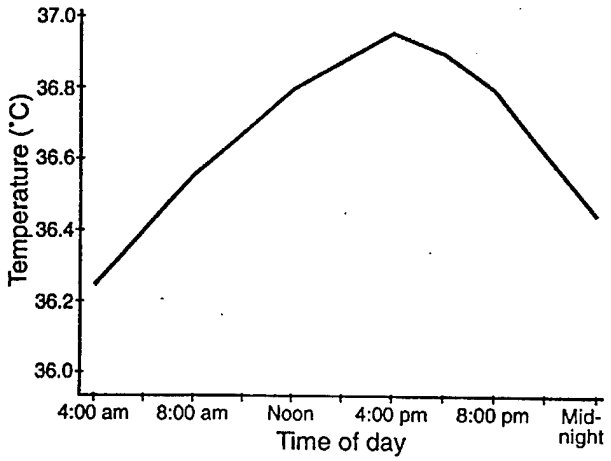

Figure 3. Effect of time of day on internal body temperature of healthy resting subjects. (Drawn from data of Mackowiak, P.A., Wasserman, and S.S., Levine, M.M. A critical appraisal of 98.6°F, the upper limit of normal body temperature, and other legacies of Carl Reinhold August Wunderlich. J. Am. Med. Assoc. 268: 1578-1580, 1992; and Stephenson, L.A., Wenger, C.B, O'Donovan, B.H., and Nadel, E.R. Circadian rhythm in sweating and cutaneous blood flow. Am. J. Physiol. 246: R321-R324, 1984.)

SKIN TEMPERATURE IS IMPORTANT IN HEAT EXCHANGE AND THERMOREGULATORY CONTROL.

Most heat is exchanged between the body and the environment at the skin surface. Skin temperature is much more variable than core temperature, and is affected by thermoregulatory responses such as skin blood flow and sweat secretion, by the temperatures of underlying tissues, and by environmental factors such as air temperature, air movement, and thermal radiation. Skin temperature, in turn, is one of the major factors determining heat exchange with the environment. For these reasons, skin temperature provides the thermoregulatory system with important information about the need to conserve or dissipate heat. Many bare nerve endings just under the skin are very sensitive to temperature. Depending on the relation of discharge rate to temperature, they are classified as either warm or cold receptors (Fig. 4), with cold receptors being about ten times as numerous as warm receptors. Furthermore, as the skin is heated warm receptors respond with a transient burst of activity, and cold receptors respond with a transient suppression; and the reverse happens as the skin is cooled. These transient responses at the beginning of heating or cooling give the central integrator almost immediate information about changes in skin temperature, and may explain, for example, the intense, brief sensation of being chilled that occurs during a plunge into cold water.

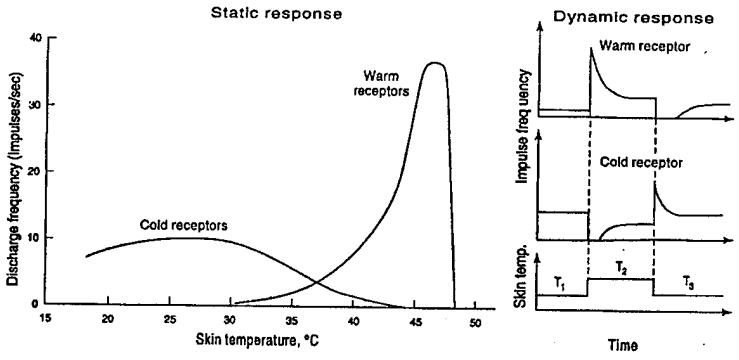

Figure 4. Responses of cold- and warm-sensitive nerve fibers in the skin. Static response (left) is the discharge frequency when skin temperature is stable. Dynamic response (right) is the discharge frequency following a change in skin temperature. (Modified from Hensel, H., and Kenshalo, D. R. Warm receptors in the nasal region of cats. J. Physiol., London 204: 99-112, 1969.)

Skin temperature usually is not uniform over the body surface, so that a mean skin temperature ($\overline{T}_{sk}$) is frequently calculated from skin temperatures measured at

several selected sites, usually weighting the temperature measured at each site according to the fraction of body surface area that it represents. It would be prohibitively invasive and difficult to measure shell temperature directly. Instead, therefore, skin temperature also is commonly used along with core temperature to calculate a mean body temperature and to estimate the quantity of heat stored in the body.

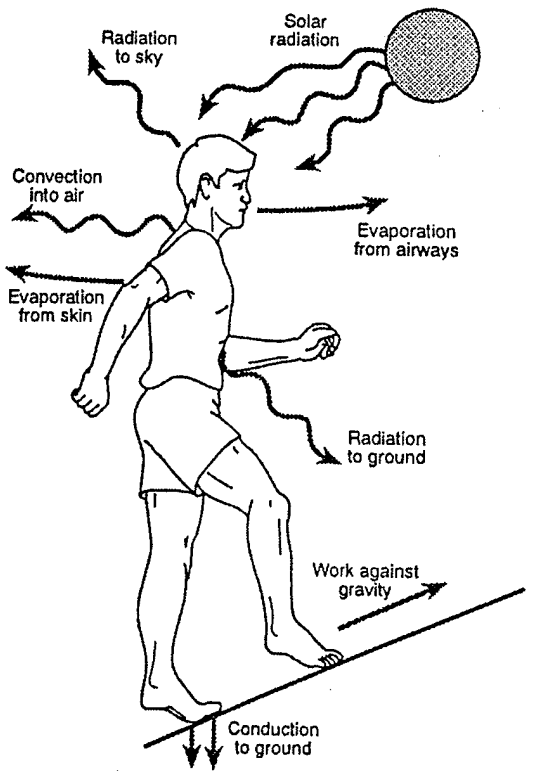

Figure 5. Exchange of energy with the environment. This hiker gains heat from the sun by radiation, and loses heat by conduction to the ground through the soles of his feet, by convection into the air, by radiation to the ground and sky, and by evaporation of water from his skin and respiratory passages. In addition, some of the energy released by his metabolic processes is converted into mechanical work, rather than heat, since he is walking uphill.

BALANCE BETWEEN HEAT PRODUCTION AND HEAT LOSS

All animals exchange energy with the environment. Some energy is exchanged as mechanical work, but most is exchanged as heat (Fig. 5). Heat is exchanged by conduction, convection, and radiation; and as latent heat through evaporation or (rarely) condensation of water. If the sum of energy production and energy gain from the environment does not equal energy loss, the extra heat is "stored" in, or lost from, the body. This is summarized in the heat balance equation

$$M = E + R + C + K + W + S \qquad (1)$$

where M is metabolic rate; E is rate of heat loss by evaporation; R and C are rates of heat loss by radiation and convection, respectively; K is the rate of heat loss by

conduction; W is rate of energy loss as mechanical work; and S is rate of heat storage in the body, manifested as changes in tissue temperatures.

M is always positive, but the terms on the right side of eq. 1 represent energy exchange with the environment and storage, and may be either positive or negative. E, R, C, K, and W are positive if they represent energy losses from the body, and negative if they represent energy gains. When $S = 0$, the body is in heat balance and body temperature neither rises nor falls. When the body is not in heat balance, its mean tissue temperature increases if S is positive, and decreases if S is negative. This commonly occurs on a short-term basis and lasts only until the body responds to changes in its temperature with thermoregulatory responses sufficient to restore balance; but if the thermal stress is too great for the thermoregulatory system to restore balance, the body will continue to gain or lose heat, until either the stress diminishes so that the thermoregulatory system can again restore the balance, or death occurs.

The traditional units for measuring heat are a potential source of confusion, since the same name, calorie, refers to two units differing by a thousand-fold. The calorie used in chemistry and physics is the quantity of heat that will raise the temperature of 1 g of pure water by 1 °C, and is also called the small calorie or gram calorie. The Calorie (capital C) used in physiology and nutrition is the quantity of heat that will raise the temperature of 1 kg of pure water by 1 °C, and is also called the large calorie, kilogram calorie, or (the usual practice in thermal physiology) the kilocalorie (kcal). Since heat is a form of energy, it is now often measured in Joules, the unit of work (1 kcal = 4186 J); and rate of heat production or heat flow in Watts, the unit of power (1 W = 1 J/s). This practice avoids confusion of small and large calories. However, kilocalories are still used widely enough that it is necessary to be familiar with them, and there is a certain advantage to a unit based on water since the body itself is mostly water.

HEAT IS A BY-PRODUCT OF ENERGY-REQUIRING METABOLIC PROCESSES.

Metabolic energy is used for active transport via membrane pumps, for energy-requiring chemical reactions such as formation of glycogen from glucose and proteins from amino acids, and for muscular work. Most of the metabolic energy used in these processes is converted into heat within the body. This may occur almost immediately,

as with energy used for active transport or with heat produced as a by-product of muscular activity. Other energy is converted to heat only after a delay, as when the Heat is a by-product of energy-requiring metabolic processes energy used in forming glycogen or protein is released as heat when the glycogen is converted back into glucose, or the protein back into amino acids.

Metabolic rate and sites of heat production at rest

Among subjects of different body size, metabolic rate at rest varies approximately in proportion to body surface area. In a resting and fasting young man it is about 45W/m^2 (81W or 70kcal/h for 1.8 m^2 body surface area), corresponding to an O_2 consumption of about 240 ml/min. About 70% of energy production at rest occurs in the body core—trunk viscera and brain—even though they comprise only about 36% of the body mass (Table 2). As a by-product of their metabolic processes these organs produce most of the heat needed to maintain heat balance at comfortable

Table 2. Relative masses and rates of metabolic heat production of various body compartments during rest and severe exercise.

	Body mass (%)	Heat production (%)	
		Rest	Exercise
Brain	2	16	1
Trunk viscera	34	56	8
Muscle and skin	56	18	90
Other	8	10	1

Modified from Wenger C.B, and Hardy J.D. Temperature regulation and exposure to heat and cold. In: Therapeutic Heat and Cold, 4th ed. (Chap. 4) J.F. Lehmann (Ed.) Baltimore: Williams and Wilkins, 150-178, 1990.

environmental temperatures, and only in the cold must such by-product heat be supplemented by heat produced expressly for thermoregulation.

Other factors besides body size that affect metabolism at rest include sex and age (Fig. 6), hormones, and digestion. The ratio of metabolic rate to surface area is highest in infancy, and then declines with age, most rapidly in childhood and adolescence and more slowly thereafter. Children have high metabolic rates in relation to surface area because of the energy used to synthesize the fats, proteins, and other tissue components needed to sustain growth. Similarly a woman's metabolic rate increases during pregnancy to supply the energy needed for the growth of the fetus. However, a non-pregnant woman's metabolic rate is 5 to 10% lower than that of a man of the same age and surface area, probably because a higher proportion of the female body is composed of fat, a tissue with low metabolism.

Catecholamines and thyroxine are the hormones having the greatest effect on metabolic rate. Catecholamines cause glycogen to break down into glucose, and stimulate many enzyme systems, thus increasing cellular metabolism; and hypermetabolism is a clinical feature of some cases of pheochromocytoma, a secreting tumor of the adrenal medulla. Thyroxine magnifies the metabolic response to catecholamines, increases protein synthesis, and stimulates oxidation by the mitochondria. Metabolic rate is typically 45% above normal in hyperthyroidism (but up to twice normal in severe cases) and 25% below normal in hypothyroidism (but 45% below normal with complete lack of thyroid hormone). Other hormones have relatively minor effects on metabolic rate.

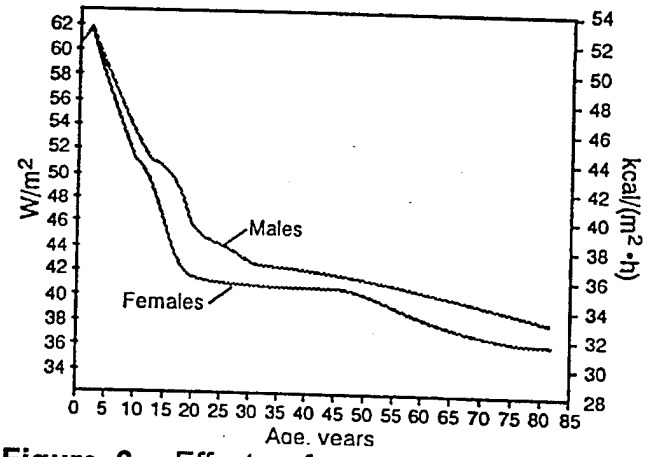

Figure 6. Effects of age and sex on basal metabolic rate of normal subjects. Metabolic rate is here expressed as the ratio of energy consumption to body surface area. (Modified from Elizondo, R.S. Regulation of body temperature. In: Human Physiology R.A. Rhoades and R.G. Pflanzer (Eds.) Philadelphia: Saunders, 823-855, 1989.)

A resting person's metabolic rate increases 10-20% after a meal. This

effect of food, called the specific dynamic action, lasts several hours. The effect is greatest after eating protein, less after carbohydrate and fat, and appears to be associated with processing the products of digestion in the liver.

Measurement of Metabolic Rate

Since so many factors affect metabolism at rest, metabolic rate is often measured under a set of standard conditions in order to compare it with established norms, and metabolic rate measured under these conditions is called basal metabolic rate (BMR). The commonly accepted conditions for measuring BMR are that the person must have fasted for 12 hours; that the measurement be made in the morning after a good night's sleep, and begin after the person has rested quietly for at least 30 minutes; and that the air temperature be comfortable, about 25°C (77°F). BMR is "basal" only during wakefulness, since metabolic rate during sleep is somewhat less than BMR.

Heat exchange with the environment can be measured directly in a human calorimeter, an insulated chamber specially constructed so that heat can leave the chamber only in the air ventilating the chamber or, often, in water flowing through a heat exchanger in the chamber. By accurately measuring the flow of air and water, and their temperatures as they enter and leave the chamber, one can accurately determine the subject's heat loss by conduction, convection and radiation; and by measuring also the moisture content of air entering and leaving the chamber one can determine heat loss by evaporation. This technique is called direct calorimetry, and though conceptually simple, it is cumbersome and costly. Metabolic rate is often estimated by indirect calorimetry, which is based on measuring a person's rate of O_2 consumption, since virtually all energy available to the body depends ultimately on reactions that consume O_2. Consumption of one liter of O_2 is associated with release of 21.1kJ (5.05kcal) if the fuel is carbohydrate, 19.8kJ (4.74kcal) if the fuel is fat, and 18.6kJ (4.46kcal) if the fuel is protein. An average value that is often used for metabolism of a mixed diet is 20.2kJ (4.83kcal) per liter of O_2. The ratio of CO_2 produced to O_2 consumed in the tissues is called the respiratory quotient (RQ). The RQ is 1.0 for oxidation of carbohydrate, 0.71 for oxidation of fat, and 0.80 for oxidation of protein. In a steady state where CO_2 is exhaled from the lungs at the same rate that it is produced in the tissues, RQ is equal to the respiratory exchange ratio, R; and one can improve the accuracy of indirect

calorimetry by also determining R, and either estimating the amount of protein oxidized—which usually is small compared to fat and carbohydrate—or calculating it from urinary nitrogen excretion.

Skeletal muscle metabolism and external work

Even during very mild exercise the muscles are the principal source of metabolic heat, and during intense exercise they may account for up to 90%. Moderately intense exercise by a healthy but sedentary young man may require a metabolic rate of 600W (in contrast to about 80W at rest); and intense activity by a trained athlete, 1400W or more. Because of their high metabolic rate, exercising muscles may be almost 1°C warmer than the core; and blood perfusing these muscles is warmed, and in turn warms the rest of the body and consequently raises core temperature. Like steam and gasoline engines, muscles convert most of the energy in the fuels that they consume into heat rather than mechanical work. During phosphorylation of ADP to form ATP, 58% of the energy released from the fuel is converted into heat, and only about 42% is captured in the ATP that is formed in the process. Then when a muscle contracts, some of the energy in the ATP that was hydrolyzed is converted into heat rather than into mechanical work. The efficiency at this stage varies enormously, and is zero in isometric muscle contraction, in which a muscle's length does not change while it develops tension, so that no work is done even though metabolic energy is required. Finally some of the mechanical work that is produced is converted by friction into heat within the body. (This is, for example, the fate of all of the mechanical work done by the heart in pumping blood.) At best, no more than one quarter of the metabolic energy released during exercise is converted into mechanical work outside the body, and the other three quarters or more is converted into heat within the body.

CONVECTION, RADIATION, AND EVAPORATION ARE THE MAIN AVENUES OF HEAT EXCHANGE WITH THE ENVIRONMENT.

Convection is transfer of heat due to movement of a fluid, either liquid or gas. In thermal physiology the fluid is usually air or water in the environment, or blood in the case of heat transfer inside the body. To illustrate, let us consider an object that is immersed in a cooler fluid. Heat passes from the object to the immediately adjacent

fluid by conduction. If the fluid is stationary, conduction is the only means by which heat can pass through the fluid, and over time the rate of heat flow from the body to the fluid will diminish as the fluid nearest the object approaches the temperature of the object. In practice, however, fluids are rarely stationary. If the fluid is moving, heat will still be carried from the object into the fluid by conduction, but once the heat has entered the fluid, it will be carried by the movement of the fluid itself—in other words, it will flow by convection. The same fluid movement that carries heat away from the surface of the object constantly brings fresh cool fluid to the surface, so that the object gives up heat to the fluid much more rapidly than if the fluid were stationary. Although conduction does play a role in this process, convection so dominates the overall heat transfer that we refer to the heat transfer as if it were entirely convection. Therefore the conduction term (*K*) in the heat balance equation is restricted to heat flow between the body and other solid objects, and usually represents only a small part of the total heat exchange with the environment.

Every surface emits energy as electromagnetic radiation with a power output proportional to the area of the surface, to the fourth power of its absolute temperature (i.e., measured from absolute zero), and to the emissivity (e) of the surface, a number between 0 and 1. (In this discussion the term "surface" has a broader meaning than usual, so that a flame and the sky, for example, are surfaces.) Such radiation, called thermal radiation, is largely in the infrared range at ordinary tissue and environmental temperatures. Most surfaces except polished metals have emissivities near 1 in this range of temperatures, and thus emit with a power output near the theoretical maximum. The emissivity of any surface is equal to the absorptivity, i.e., the fraction of incident radiant energy that the surface absorbs. (For this reason an ideal emitter is called a black body.) If two bodies exchange heat by thermal radiation, radiation travels in both directions; but since each body emits radiation with an intensity that depends on its temperature, the net heat flow is from the warmer to the cooler body.

When a gram of water is converted into vapor at 30°C, it absorbs 2425J (0.58 kcal), the latent heat of evaporation, in the process. Evaporation of water is thus an efficient way of losing heat; and it is the body's only means of losing heat when the environment is hotter than the skin, as it usually is when the environment is warmer than 36°C. Evaporation must then dissipate both the metabolic heat and any heat

gained from the environment by convection and radiation. Most water evaporated in the heat comes from sweat; but even in the cold the skin loses some water by evaporation of insensible perspiration, i.e. water that diffuses through the skin rather than being secreted. In eq. 1 *E* is nearly always positive, representing heat loss from the body. However *E* is negative in the rare circumstances (e.g., in a steam room) in which water vapor gives up heat to the body by condensing on the skin.

HEAT EXCHANGE IS PROPORTIONAL TO SURFACE AREA AND OBEYS BIOPHYSICAL PRINCIPLES.

Animals exchange heat with their environment through both skin and respiratory passages, but only the skin exchanges heat by radiation. In panting animals respiratory heat loss may be large, and may be an important means of achieving heat balance. In humans, however, respiratory heat exchange is usually relatively small and (though hyperthermic subjects may hyperventilate) is not predominantly under thermoregulatory control, and we will not consider it further.

Convective heat exchange between the skin and the environment is proportional to the difference between skin and ambient air temperatures, as expressed by the equation

$$C = h_c \cdot A \cdot (\overline{T}_{sk} - T_a) \qquad (2)$$

where A is the body surface area, $\overline{T}_{sk}$ and T_a are mean skin and ambient temperatures, and h_c is the convective heat transfer coefficient. h_c includes the effects of the factors other than temperature and surface area, that affect convective heat exchange. For the whole body, air movement is the most important of these factors, and convective heat exchange (and thus h_c) varies approximately as the square root of the air speed (Fig. 7). Other factors that affect h_c include the direction of the air movement and the curvature of the skin surface. As the radius of curvature decreases, h_c increases, so that the hands and fingers are effective in convective heat exchange out of proportion to their surface area.

Radiative heat exchange is proportional to the difference between the fourth powers of the absolute temperatures of the skin and of the radiant environment (T_r),

and to the emissivity of the skin (e_{sk}): i.e., $R \propto e_{sk} \cdot (\bar{T}_{sk}^4 - T_r^4)$. However if T_r is close enough to $\bar{T}_{sk}$ that $\bar{T}_{sk}-T_r$ is much smaller than the absolute temperature of the skin, R is nearly proportional to $e_{sk} \cdot (\bar{T}_{sk}-T_r)$. Some parts of the body surface (e.g., inner surfaces of the thighs and arms) exchange heat by radiation with other parts of the body surface, so that the body exchanges heat with the environment as if it had an area smaller than its actual surface area. This smaller area is called the effective radiating surface area (A_r), and depends on the posture, being closest to the actual surface area in a "spread eagle" posture, and least in someone curled up. Radiative heat exchange can be represented by the equation

$$R = h_r \cdot e_{sk} \cdot A_r \cdot (\bar{T}_{sk}-T_r) \tag{3}$$

where h_r is the radiant heat transfer coefficient, 6.43 W/($m^2 \cdot$°C) at 28°C.

Evaporative heat loss from the skin to the environment is proportional to the difference between the water vapor pressure at the skin surface and the water vapor pressure in the ambient air. These relations are summarized in the following equation:

$$E = h_e \cdot A \cdot (P_{sk}-P_a) \tag{4a}$$

where P_{sk} is the water vapor pressure at the skin surface, P_a is the ambient water vapor pressure, and h_e is the evaporative heat transfer coefficient.
Water vapor, like heat, is carried away by moving air, so that geometrical factors and air movement affect E and h_e in just the same way as they affect C and h_c. If the skin is completely wet, the water vapor pressure at the skin surface is the saturation water vapor pressure (Fig. 8) at skin temperature, and evaporative heat loss is E_{max}, the maximum possible for the prevailing skin temperature and environmental conditions. This condition is described in eq. 4b:

$$E_{max} = h_e \cdot A \cdot (P_{sk,sat}-P_a) \tag{4b}$$

where $P_{sk,sat}$ is the saturation water vapor pressure at skin temperature.
When the skin is not completely wet, it is impractical to measure P_{sk}, the actual average water vapor pressure at the skin surface. Therefore a coefficient called skin wettedness

(w) is defined as the ratio E/E_{max}, with $0 \leq w \leq 1$. Skin wettedness depends on the hydration of the epidermis and the fraction of the skin surface that is wet. We can now re-write eq. 4a as:

$$E = h_e \cdot A \cdot w \cdot (P_{sk,sat} - P_a) \qquad (4c)$$

Wettedness depends on the balance between secretion and evaporation of sweat. If secretion exceeds evaporation, sweat accumulates on the skin and spreads out to wet more of the space between neighboring sweat glands, so increasing wettedness and E; and if evaporation exceeds secretion, the reverse occurs. If sweat rate exceeds E_{max}, then once wettedness becomes 1, the excess sweat drips from the body since it cannot evaporate.

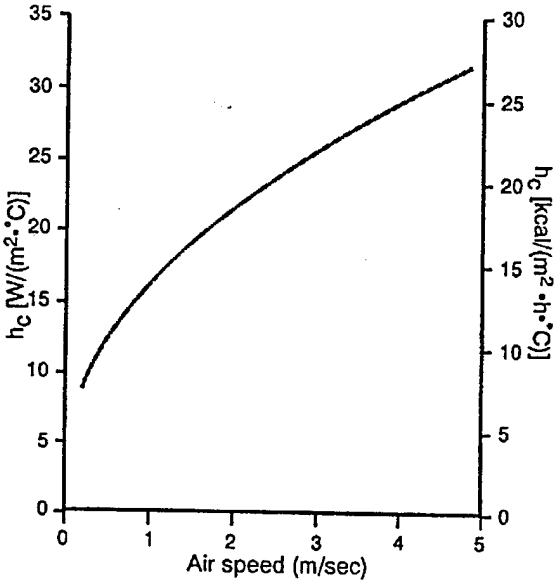

Figure 7. The convective heat transfer coefficient, h_c, for a standing human as a function of air speed. The horizontal axis can be converted into English units by using the relation 5 m/s = 16.4 ft/s = 11.2 mph. The evaporative heat transfer coefficient, h_e, also increases with air speed, and $h_e = h_c \cdot 2.2$ °C/mmHg.

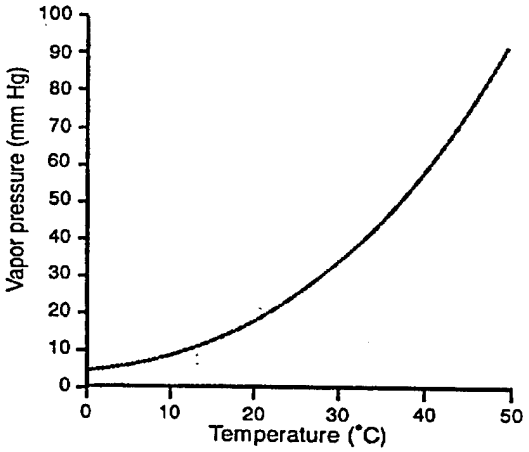

Figure 8. The saturation vapor pressure of water as a function of temperature. For any given temperature, the water vapor pressure is at its saturation value when the air is "saturated" with water vapor—i.e., holds the maximum amount possible at that temperature.

Note that P_a, on which evaporation from the skin directly depends, is proportional to the actual moisture content in the air. By contrast the more familiar quantity relative

humidity (rh) is the ratio between the actual moisture content in the air and the maximum moisture content that is possible at the temperature of the air. It is important to recognize that rh is only indirectly related to evaporation from the skin. For example in a cold environment, P_a will be low enough that sweat can easily evaporate from the skin even if rh = 100%.

A detailed discussion of clothing is beyond the scope of this report, but it should be obvious that clothing reduces heat exchange between the body and its environment. Clothing impedes air movement, thus reducing h_c and h_e at the skin and thereby reducing heat exchange by convection and evaporation. In addition, clothing resists conduction of heat, and is at least a partial barrier to electromagnetic radiation and passage of water vapor. For all of these reasons, clothing creates a microenvironment which is closer to skin temperature than is the environment outside the clothing. Furthermore, since the body is a source of water vapor, the air inside the clothing is more humid than outside. The conditions inside this microenvironment—air temperature, water vapor pressure, and temperature of the inner surface of the clothing—are what determine heat gain or heat loss from unexposed skin. These conditions in turn are determined by the conditions outside the clothing, the properties of the clothing, and the rate at which the body releases heat and moisture into this microenvironment. Therefore a person's level of physical activity determines both the appropriate level of clothing for a given set of environmental conditions, and the degree of heat strain that would result from wearing clothing that is too warm for the conditions, as is frequently the case with protective clothing. Thus the oft-cited rule that wearing protective clothing in MOPP IV configuration is equivalent to adding 10°F to the Wet-Bulb Globe Temperature, though approximately correct for moderate levels of exercise and humidity, may lead to a serious underestimate of the heat strain occurring during heavy exercise or in conditions that require a high rate of evaporative heat loss. Although clothing reduces heat exchange between covered skin and the environment, it generally has little effect on heat exchange of exposed skin. Therefore—especially when the clothing is heavy and most of the skin is covered—exposed skin may account for a fraction of the body's heat loss that far exceeds the exposed fraction of the body's surface. Thus in the cold, a bare head may account for half of the heat loss from the body; and in someone exercising while wearing protective clothing in MOPP III

configuration (full protective gear except gas mask and hood), donning the mask and hood while continuing to exercise may lead to a dramatic increase in heat strain.

HEAT STORAGE IS A CHANGE IN THE HEAT CONTENT OF THE BODY.

The rate of heat storage is the difference between heat production/gain and heat loss (Eq. 1), and can be determined experimentally from simultaneous measurements of metabolism by indirect calorimetry and heat gain or loss by direct calorimetry. Storage of heat in the tissues changes their temperature, and the amount of heat stored is the product of body mass, the body's mean specific heat, and a suitable mean body temperature (T_b). The body's mean specific heat depends on its composition, especially the proportion of fat, and is about 3.55kJ/(kg·°C) [0.85kcal/(kg·°C)]. Empirical relations of T_b to core temperature (T_c) and $\bar{T}_{sk}$, determined in calorimetric studies, depend on ambient temperature, with T_b varying from $0.65 \cdot T_c + 0.35 \cdot \bar{T}_{sk}$ in the cold to $0.9 \cdot T_c + 0.1 \cdot \bar{T}_{sk}$ in the heat. The shift from cold to heat in the relative weighting of T_c and $\bar{T}_{sk}$ reflects the accompanying change in the thickness of the shell (Fig. 2).

HEAT DISSIPATION

Figure 9 shows rectal and mean skin temperatures, heat losses, and calculated shell conductances for nude resting men and women at the end of 2-hour exposures in a calorimeter to ambient temperatures from 23 to 36°C. Shell conductance represents the sum of heat transfer by two parallel modes, i.e. conduction through the tissues of the shell, and convection by the blood; and it is calculated by dividing heat loss through the skin (HF_{sk})—i.e., total heat loss less heat loss through the respiratory tract—by the difference between core and mean skin temperatures, as follows:

$$C = HF_{sk}/(T_c - \bar{T}_{sk}) \qquad (5)$$

where C is shell conductance, and T_c and $\bar{T}_{sk}$ are core and mean skin temperatures.

From 23 to 28°C these subjects' conductance is minimal, because their skin is vasoconstricted and its blood flow is quite low. The minimal level of conductance attainable depends largely on the thickness of the subcutaneous fat layer, and the

women's thicker layer allows them to attain a lower conductance than men. At about 28°C conductance begins to increase, and above 30°C conductance continues to increase and sweating begins.

For these nude subjects, the range 28-30°C is the zone of thermoneutrality, i.e., the range of comfortable environmental temperatures in which thermal balance is maintained without either shivering or sweating. In this zone heat balance is maintained entirely by controlling conductance and $\overline{T}_{sk}$, and thus *R* and *C*. As equations 2-4a show, *C*, *R*, and *E* all depend on skin temperature, which, in turn, depends partly on skin blood flow. *E* depends also, through skin wettedness, on sweat secretion. Thus all these modes of heat exchange are partly under physiological control.

EVAPORATION OF SWEAT CAN DISSIPATE LARGE AMOUNTS OF HEAT.

In Fig. 9 evaporative heat loss is nearly independent of ambient temperature below 30°C, and is 9-10 W/m^2, corresponding to evaporation of about 13-15 gm/(m^2·h), of which about half is moisture lost in breathing and half is

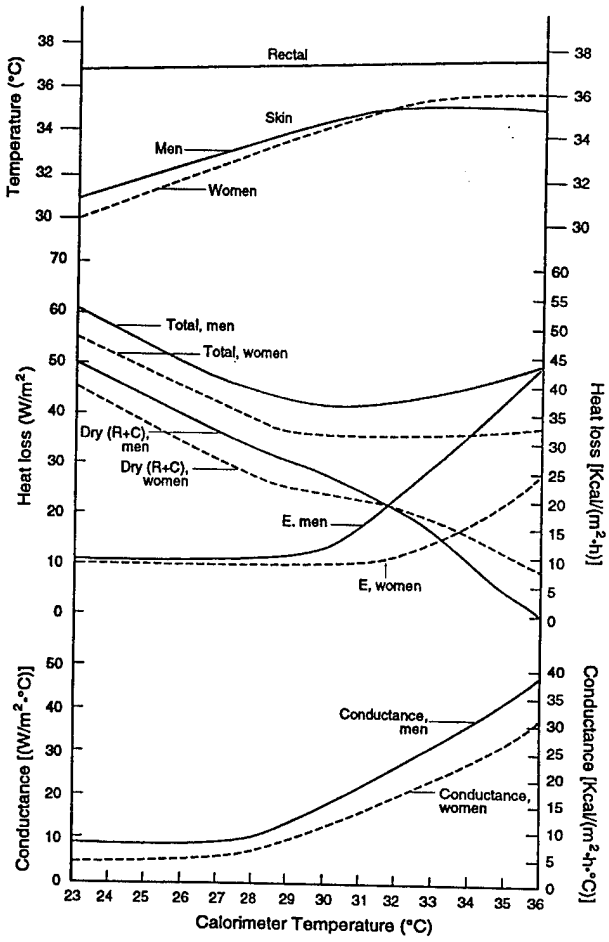

Figure 9. Average values of rectal and mean skin temperatures, heat loss, and core-to-skin thermal conductance for nude resting men and women near steady state after two hours at different environmental temperatures in a calorimeter. (All energy-exchange quantities in this figure have been divided by body surface area, to remove the effect of individual body size.) Total heat loss is the sum of dry heat loss [by radiation (*R*) and convection (*C*)] and evaporative heat loss (*E*). Dry heat loss is proportional to the difference between skin temperature and calorimeter temperature, and it decreases with increasing calorimeter temperature. (Redrawn from data of Hardy, J.D. and DuBois, E.F. Differences between men and women in their response to heat and cold. Proc. Natl. Acad. Sci. US 26: 389-398, 1940.)

insensible perspiration. This evaporation occurs independently of thermoregulatory control. As the ambient temperature increases, the body depends more and more on evaporation of sweat to achieve heat balance.

There are two histological types of sweat glands, eccrine and apocrine. In northern Europeans, apocrine glands are found mostly in the axilla and in pigmented skin, such as on the lips; but they are more widely distributed in some other populations. Eccrine sweat is essentially a dilute electrolyte solution, but apocrine sweat also contains fatty material. Eccrine sweat glands, the dominant type in all human populations, are the more important in human thermoregulation, and number about 2,500,000. They are controlled through postganglionic sympathetic nerves which release acetylcholine rather than norepinephrine. A healthy man unacclimatized to heat can secrete up to 1.5 liters of sweat per hour. Although the number of functional sweat glands is fixed before the age of three, the secretory capacity of the individual glands can change, especially with endurance exercise training and heat acclimatization; and a man well acclimatized to heat can secrete as much as 2.5 liters per hour. Such rates cannot be maintained, however, and the maximum daily sweat rate is probably 12-15 liters.

The sodium concentration of eccrine sweat ranges from less than 5 to 60 mEq/L (versus 135 to 145 mEq/L in plasma); but even at 60 mEq/L, sweat is the most dilute body fluid. In producing sweat that is hypotonic to plasma, the glands reabsorb sodium from the sweat duct by active transport. As sweat rate increases, the rate at which the glands reabsorb sodium increases more slowly, so that sodium concentration in the sweat increases. The sodium concentration of sweat is affected also by heat acclimatization and the action of mineralocorticoids. Cystic fibrosis impairs the sweat glands' ability to conserve sodium, apparently through a defect in chloride ion transport. Sodium and chloride concentrations in the sweat of cystic fibrosis patients, though still lower than in plasma, are substantially higher than normal and provide the basis for a clinical test: sweat concentrations of sodium or chloride above 60 meq/L in children (70 meq/L in adults) are considered diagnostic of cystic fibrosis.

SKIN CIRCULATION IS IMPORTANT IN HEAT TRANSFER.

Heat produced within the body must be delivered to the skin surface to be eliminated. When skin blood flow is minimal, core-to-skin thermal conductance (i.e., the conductance of the shell) is typically 5-9 W/°C per m^2 of body surface. For a lean resting subject with a surface area of $1.8m^2$, minimal whole-body conductance of 16W/°C [i.e., $8.9W/(°C \cdot m^2) \times 1.8m^2$] and a metabolic heat production of 80W, the temperature difference between core and skin must be 5°C (i.e., 80W ÷ 16W/°C) for the heat produced to be conducted to the surface. In a cool environment, T_{sk} may easily be low enough for this to occur. However, in an ambient temperature of 33°C $\bar{T}_{sk}$ is typically about 35°C; and without an increase in conductance, core temperature would have to rise to 40°C—a high though not yet dangerous level—for the heat to be conducted to the skin. If the rate of heat production were increased to 480W by moderate exercise, the temperature difference between core and skin would have to rise to 30°C—and core temperature to well beyond lethal levels—to allow all the heat produced to be conducted to the skin. In these latter circumstances, the conductance of the shell must increase greatly in order for the body to re-establish thermal balance and continue to regulate its temperature; and this is accomplished by increasing skin blood flow.

The effectiveness of skin blood flow in heat transfer

If we assume that blood on its way to the skin remains at core temperature until it reaches the skin, comes to skin temperature as it passes through the skin, and then stays at skin temperature until it returns to the core, we can compute the rate of heat flow (HF_b) due to convection by the blood as:

$$HF_b = SkBF \cdot (T_c - T_{sk}) \cdot 3.85kJ/(L \cdot °C) \quad (6)$$

where SkBF = rate of skin blood flow, expressed in L/s rather than the more usual L/min, to simplify computing HF in W (i.e., J/s); and 3.85kJ/(L·°C) [0.92kcal/(L·°C)] = volume specific heat of blood.

Conductance due to convection by the blood (C_b) is calculated as:

$$C_b = HF_b/(T_c-T_{sk}) = SkBF \cdot 3.85kJ/(L \cdot °C) \quad (7)$$

Of course, heat continues to flow by conduction through the tissues of the shell, so that total conductance is the sum of conductance due to convection by the blood plus that due to conduction through the tissues; and total heat flow is given by:

$$HF = (C_b+C_0) \cdot (T_c-T_{sk}) \quad (8)$$

in which C_0 is thermal conductance of the tissues when skin blood flow is minimal, and thus is due predominantly to conduction through the tissues.

The assumptions made in deriving eq. 6 are somewhat artificial, and represent the conditions for maximum efficiency of heat transfer by the blood. In practice blood exchanges heat also with the tissues through which it passes on its way to and from the skin. Heat exchange with these other tissues is greatest when skin blood flow is low, and in such cases heat flow to the skin may be much less that predicted by eq. 6 discussed further below). However, eq. 6 is a reasonable approximation in a warm subject with moderate to high skin blood flow. It is not possible to measure whole-body SkBF directly, but it is believed to reach several liters a minute during heavy exercise in the heat; and the maximum obtainable is estimated to be nearly 8 L/min. If SkBF = 1.89L/min (0.0315L/s), then according to eq. 7 skin blood flow contributes about 121W/°C to the conductance of the shell. If conduction through the tissues contributes 16W/°C, total shell conductance is 137W/°C; and if T_c = 38.5°C and T_{sk} = 35°C, then this will produce a core-to-skin heat transfer of 480W, the heat production in our earlier example of moderate exercise. Thus even a moderate rate of skin blood flow can have a dramatic effect on heat transfer.

When a person is not sweating, raising skin blood flow brings skin temperature nearer to blood temperature, and lowering skin blood flow brings skin temperature nearer to ambient temperature. Under such conditions the body is able to control dry (convective and radiative) heat loss by varying skin blood flow and thus skin temperature. Once sweating begins, skin blood flow continues to increase as the person becomes warmer, but in these conditions the tendency of an increase in skin blood flow to warm the skin is approximately balanced by the tendency of an increase

in sweating to cool the skin. Therefore after sweating has begun, further increases in skin blood flow usually cause little change in skin temperature or dry heat exchange, and serve primarily to deliver to the skin the heat that is being removed by evaporation of sweat. Skin blood flow and sweating thus work in tandem to dissipate heat under such conditions.

Sympathetic control of skin circulation

Blood flow in human skin is under dual vasomotor control. In most of the skin the vasodilation that occurs during heat exposure depends on sympathetic nervous signals that cause the blood vessels to dilate, and this vasodilation can be prevented or reversed by regional nerve block. Since it depends on the action of nervous signals, such vasodilation is sometimes referred to as active vasodilation. Active vasodilation occurs in almost all the skin except in the so-called acral regions—hands, feet, lips, ears, and nose. In the skin areas where active vasodilation occurs, vasoconstrictor activity is minimal at thermoneutral temperatures, and active vasodilation during heat exposure does not begin until close to the onset of sweating. Thus skin blood flow in these areas is not much affected by small temperature changes within the thermoneutral range. The neurotransmitter or other vasoactive substance responsible for active vasodilation in human skin has not been identified. However, since sweating and vasodilation operate in tandem in the heat, some investigators have proposed that the mechanism for active vasodilation is somehow linked to the action of sweat glands.

Reflex vasoconstriction, occurring in response to cold and also as part of certain non-thermal reflexes such as baroreflexes, is mediated primarily through adrenergic sympathetic fibers which are distributed widely over most of the skin. Reducing the flow of impulses in these nerve fibers allows the blood vessels to dilate. In the acral regions and in the superficial veins (whose role in heat transfer is discussed below), vasoconstrictor fibers are the predominant vasomotor innervation, and the vasodilation that occurs during heat exposure is largely a result of the withdrawal of vasoconstrictor activity. Blood flow in these skin regions is sensitive to small temperature changes even in the thermoneutral range, and may be responsible for "fine tuning" heat loss to maintain heat balance in this range.

THERMOREGULATORY CONTROL

In discussions of control systems the words regulation and regulate have meanings distinct from those of control. The variable which a control system acts to maintain within narrow limits (e.g., temperature) is called the regulated variable, and the quantities which it controls in order to accomplish this (e.g., sweating rate, skin blood flow, metabolic rate, and thermoregulatory behavior) are called controlled variables.

Human beings have two distinct sub-systems to regulate body temperature: behavioral thermoregulation and physiological thermoregulation. Physiological thermoregulation is capable of fairly precise adjustments of heat balance, but is effective only within a relatively narrow range of environmental temperatures. On the other hand behavioral thermoregulation, through the use of shelter and space heating and clothing, enables humans to live in the most extreme climates on earth; but behavioral thermoregulation does not provide fine control of body heat balance.

BEHAVIORAL THERMOREGULATION IS GOVERNED BY THERMAL SENSATION AND COMFORT.

Sensory information about body temperatures is an essential part of both behavioral and physiological thermoregulation. The distinguishing feature of behavioral thermoregulation is the involvement of consciously directed effort to regulate body temperature. Thermal discomfort provides the necessary motivation for thermoregulatory behavior, and behavioral thermoregulation acts to reduce both the discomfort and the physiological burden imposed by a stressful thermal environment. For this reason the zone of thermoneutrality is characterized both by thermal comfort and by the absence of shivering and sweating.

Warmth and cold on the skin are felt as either comfortable or uncomfortable, depending on whether they decrease or increase the physiological strain. Thus a shower temperature that feels pleasant after strenuous exercise may be uncomfortably chilly on a cold winter morning. The processing of thermal information in behavioral thermoregulation is not as well understood as it is in physiological thermoregulation. However, perceptions of thermal sensation and comfort respond much more quickly

than either core temperature or physiological thermoregulatory responses to changes in environmental temperature, and thus appear to anticipate changes in the body's thermal state. Such an anticipatory feature would be advantageous, since it would reduce the need for frequent small behavioral adjustments.

PHYSIOLOGICAL THERMOREGULATION OPERATES THROUGH GRADED CONTROL OF HEAT-PRODUCTION AND HEAT-LOSS RESPONSES.

Familiar non-living control systems, such as most refrigerators and heating and air-conditioning systems, operate at only two levels—on and off. In a steam heating system, for example, when indoor temperature falls below the desired level, the thermostat turns on the burner under the boiler; and when the temperature is restored to the desired level, the thermostat turns the burner off. Rather than operating at only two levels, on and off, most physiological control systems produce a graded response according to the size of the disturbance in the regulated variable. In many instances, changes in the controlled variables are proportional to displacements of the regulated variable from some threshold value, and such control systems are called proportional control systems.

The control of heat-dissipating responses is an example of a proportional control system. Figure 10 shows how reflex control of two heat-dissipating responses, sweating and skin blood flow, depends on body core temperature and mean skin temperature. Each response has a core-temperature threshold, a temperature at which the response starts to increase; and these thresholds depend on mean skin temperature. Thus at any given skin temperature, the change in each response is proportional to the change in core temperature; and increasing the skin temperature lowers the threshold level of core temperature and increases the response at any given core temperature. In humans a change of 1°C in core temperature elicits about nine times as great a thermoregulatory response as a 1°C change in mean skin temperature. (Besides its effect on the reflex signals, skin temperature has a local effect that modifies the response of the blood vessels and sweat glands to the reflex signal, as we shall discuss later.)

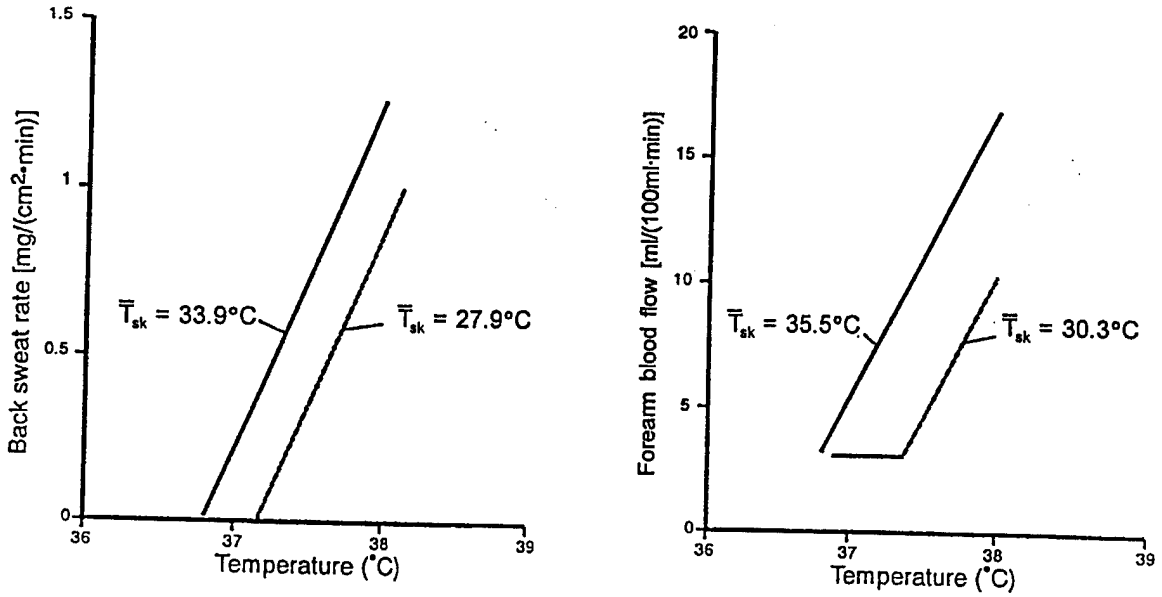

Figure 10. The relations of back (scapular) sweat rate (left) and forearm blood flow (right) to core temperature and mean skin temperature ($\bar{T}_{sk}$). In the experiments shown, core temperature was increased by exercise. (Left panel drawn from data of Sawka, M.N., Gonzalez, R.R., Drolet, L.L., and Pandolf, K.B. Heat exchange during upper- and lower-body exercise. J. Appl. Physiol. 57: 1050-1054, 1984. Right panel redrawn from Wenger, C.B., Roberts, M.F., Stolwijk, J.A.J., and Nadel, E.R. Forearm blood flow during body temperature transients produced by leg exercise. J. Appl. Physiol. 38: 58-63, 1975.)

Cold stress elicits increases in metabolic heat production through shivering and through non-shivering thermogenesis. Shivering is a rhythmic oscillating tremor of skeletal muscles. The primary motor center for shivering lies in the dorsomedial part of the posterior hypothalamus, and is normally inhibited by signals of warmth from the preoptic area of the hypothalamus. In the cold, these inhibitory signals are withdrawn, and the primary motor center for shivering sends impulses down the brainstem and lateral columns of the spinal cord, to anterior motor neurons. These impulses are not rhythmic themselves, but increase the tone of the muscles. The increased tone itself increases metabolic rate somewhat. Once tone exceeds a critical level, contraction of one group of muscle fibers stretches the muscle spindles in other groups of fibers in series with it, eliciting contractions from those groups of fibers via the stretch reflex, and so on; and thus the rhythmic oscillations characteristic of frank shivering begin. Shivering tends to occur in bursts, and the "shivering pathway" is inhibited by signals from the cerebral cortex, so that voluntary muscular activity and attention suppress shivering. Since the limbs are part of the shell in the cold, there is a preferential

recruitment of trunk and neck muscles for shivering (so-called centralization of shivering), to help retain the heat produced during shivering within the body core; and it is a familiar experience that "chattering" of the teeth is one of the earliest signs of shivering. As with the heat-dissipating responses, control of shivering depends on both core and skin temperature. However, the details of its control in terms of these temperatures are not precisely understood.

In most laboratory mammals chronic cold exposure also causes non-shivering thermogenesis, an increase in metabolic rate that is not due to skeletal muscle activity. Non-shivering thermogenesis appears to be elicited through sympathetic stimulation and circulating catecholamines. It occurs in many tissues, especially the liver and brown fat, a tissue specialized for non-shivering thermogenesis whose color is imparted by high concentrations of iron-containing respiratory enzymes. Brown fat is found in human infants, and non-shivering thermogenesis is important for their thermoregulation. In human adults, however, the existence of brown fat and non-shivering thermogenesis is controversial, even though catecholamines do have a thermogenic effect.

THE CENTRAL NERVOUS SYSTEM INTEGRATES THERMAL INFORMATION FROM CORE AND SKIN.

Temperature receptors in the body core and the skin transmit information about their temperatures through afferent nerves to the brain stem, and especially the hypothalamus, where much of the integration of temperature information occurs. The sensitivity of the thermoregulatory responses to core temperature allows the thermoregulatory system to adjust heat production and heat loss to resist disturbances in core temperature. Their sensitivity to mean skin temperature allows the system to respond appropriately to mild heat or cold exposure with little change in body core temperature, so that changes in body heat content due to changes in environmental temperature take place almost entirely in the peripheral tissues, as shown in Figure 2. For example, the skin temperature of someone who enters a hot environment rises and elicits sweating even if there is no change in core temperature. On the other hand, an increase in heat production within the body, as occurs during exercise, elicits the appropriate heat-dissipating responses through a rise in core temperature.

Core temperature receptors that participate in the control of thermoregulatory responses are very unevenly distributed, and are concentrated in the hypothalamus. In experimental mammals, temperature changes of only a few tenths of 1°C in the anterior preoptic area of the hypothalamus elicit changes in the thermoregulatory effector responses, and this area contains many neurons which increase their firing rate either in response to warming or in response to cooling. Thermal receptors have been reported elsewhere in the core of laboratory animals, including the heart, pulmonary vessels, and spinal cord; but the thermoregulatory role of core thermal receptors outside the central nervous system is not known.

Let us consider what happens when some disturbance—say, an increase in metabolic heat production due to exercise—upsets the thermal balance. Additional heat is stored in the body, and core temperature rises. The thermoregulatory controller receives information about these changes from the thermal receptors, and responds by calling forth appropriate heat-dissipating responses. Core temperature continues to rise, and these responses continue to increase, until they are sufficient to dissipate heat as fast as it is being produced, thus restoring heat balance and preventing further increases in body temperatures. In the language of control theory, the rise in core temperature which elicits heat-dissipating responses sufficient to re-establish thermal balance during exercise is an example of a load error; a load error is characteristic of any proportional control system that is resisting the effect of some imposed disturbance or "load". Although the disturbance in this example was exercise, parallel arguments apply if the disturbance is a decrease in metabolic rate or a change in the environment, except that if the disturbance is in the environment most of the temperature change will be in the skin and shell rather than in the core; and if the disturbance produces a net loss of heat, the body will restore heat balance by decreasing heat loss and increasing heat production.

The relation of controlling signal to thermal integration and set point

Both sweating and skin blood flow depend on core and skin temperatures in the same way, and changes in the threshold for sweating are accompanied by similar changes in the threshold for vasodilation. We may therefore think of the central integrator (Fig. 11) as generating one thermal command signal for the control of both

sweating and skin blood flow. This signal is based on the information about core and skin temperatures that the integrator receives, and on the thermoregulatory set point. We may think of the set point integrator (Fig. 11) as generating one thermal command signal for the control of both sweating and skin blood flow. This signal is based on the information about core and skin temperatures that the integrator receives, and on the thermoregulatory set point. We may think of the set point as the target level of core temperature, or the setting of the body's "thermostat". In the operation of the thermoregulatory system, it is a reference point which determines the thresholds of all the thermoregulatory responses. Shivering and thermal comfort are affected by changes in the set point in the same way as sweating and skin blood flow. However, we

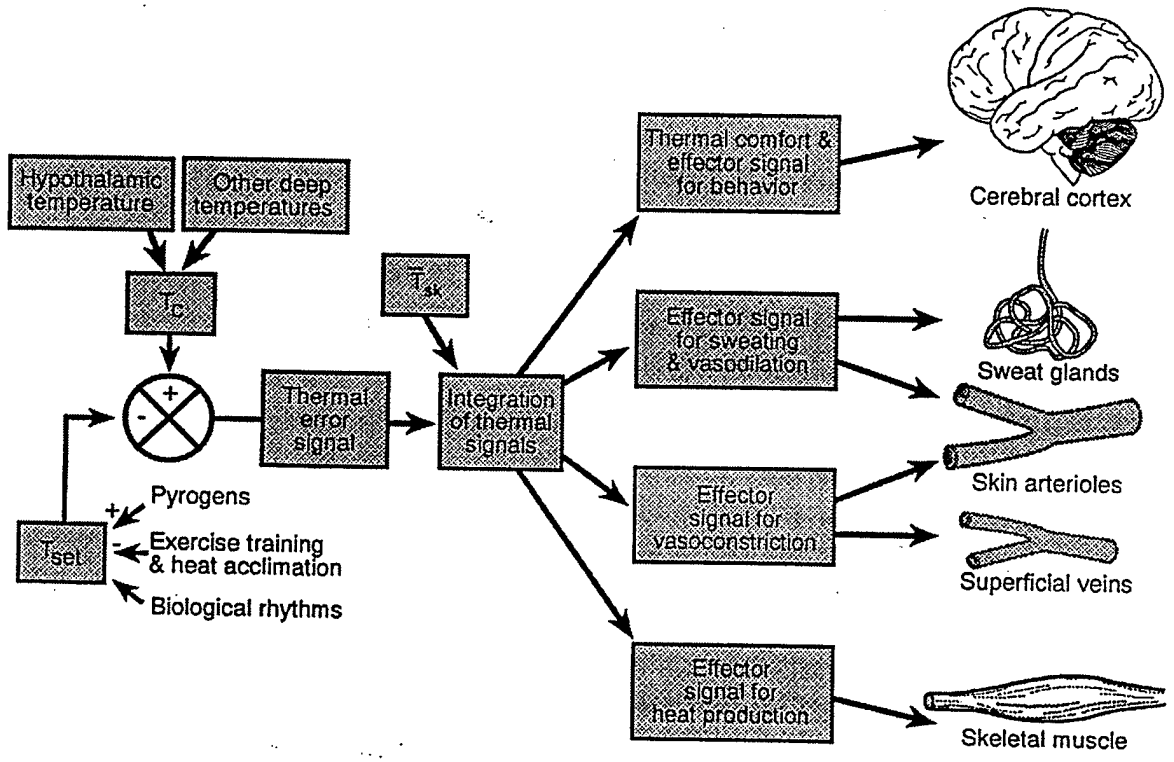

Figure 11. Schematic diagram of the control of human thermoregulatory responses. The signs by the inputs to T_{set} indicate that pyrogens raise the set point, and heat acclimation lowers it. Core temperature, T_c, is compared with the set point, T_{set}, to generate an error signal, which is integrated with thermal input from the skin to produce effector signals for the thermoregulatory responses. (Modified from Sawka, M.N., and Wenger, C.B. Physiological responses to acute exercise-heat stress. In: Human Performance Physiology and Environmental Medicine at Terrestrial Extremes (Chap. 3) K.B Pandolf, M.N. Sawka, and R.R. Gonzalez (eds), Indianapolis: Benchmark, 97-151, 1988.

do not understand the control of shivering well enough to say whether or not it is controlled by the same command signal as sweating and skin blood flow. (Thermal comfort, as we saw earlier, seems not to be controlled by the same command signal.)

The effect of non-thermal inputs on thermoregulatory responses

Each of the thermoregulatory responses may be affected by other inputs besides body temperatures and factors that affect the thermoregulatory set point. We have already noted that voluntary activity affects shivering, and certain hormones affect metabolic heat production. In addition, non-thermal factors may produce a burst of sweating at the beginning of exercise; and emotional effects on sweating and skin blood flow are matters of common experience. Skin blood flow is the thermoregulatory response most affected by non-thermal factors, because of its involvement in reflexes which function to maintain cardiac output, blood pressure, and tissue O_2 delivery during heat stress, postural changes, and hemorrhage, and sometimes during exercise, especially in the heat.

PHYSIOLOGICAL AND PATHOLOGICAL INFLUENCES MAY CHANGE THE THERMOREGULATORY SET POINT.

Fever elevates core temperature at rest, heat acclimatization decreases it, and time of day and phase of the menstrual cycle change it in a cyclical fashion. Core temperature at rest varies in an approximately sinusoidal fashion with time of day. The minimum temperature occurs at night, several hours before awaking, and the maximum, which is 0.5 to 1 °C higher, occurs in the late afternoon or evening (Fig. 3). This pattern coincides with patterns of activity and eating, but does not depend on them, and occurs even during bed rest in fasting subjects. This pattern is an example of a circadian rhythm, i.e., a rhythmic pattern in a physiological function with a period of about one day. During the menstrual cycle core temperature is at its lowest point just before ovulation, and over the next few days rises 0.5 to 1 °C to a plateau which persists through most of the luteal phase. Each of these factors—fever, heat acclimatization, the circadian rhythm, and the menstrual cycle—changes the core

temperature at rest by changing the thermoregulatory set point, thus producing corresponding changes in the thresholds for all the thermoregulatory responses.

PERIPHERAL FACTORS MODIFY THE RESPONSES OF SKIN BLOOD VESSELS AND SWEAT GLANDS.

The skin is the organ most directly affected by environmental temperature, and skin temperature affects heat loss responses not only through the reflex actions shown in Fig. 10 but also through direct effects on the effectors themselves.

Skin temperature and cutaneous vascular and sweat-gland responses

Local temperature changes act on skin blood vessels in at least two ways. First, local cooling potentiates (and heating weakens) the constriction of blood vessels in response to nervous signals and vasoconstrictor substances. (At very low temperatures, however, cold-induced vasodilation increases skin blood flow. See below.) Second, in skin regions where active vasodilation occurs, local heating causes vasodilation (and local cooling causes vasoconstriction) through a direct action on the vessels themselves, independent of nervous signals. The local vasodilator effect of skin temperature is especially strong above 35°C; and when the skin is warmer than the blood, increased blood flow helps to cool the skin and protect it from heat injury, unless this response has been impaired by vascular disease. Local thermal effects on sweat glands parallel those on blood vessels, so that local heating potentiates (and local cooling diminishes) the local sweat gland response to reflex stimulation or to acetylcholine, and intense local heating elicits sweating directly, even in sympathectomized skin.

Skin wettedness and the sweat gland response

During prolonged (several hours) heat exposure with high sweat output, sweat rates gradually decline and the sweat glands' response to local application of cholinergic drugs is also reduced. This reduction of sweat-gland responsiveness is sometimes called sweat-gland "fatigue". Wetting the skin makes the stratum corneum

swell, mechanically obstructing the sweat duct and causing a reduction in sweat secretion, an effect called hidromeiosis. The glands' responsiveness can be at least partly restored if air movement increases or humidity is reduced so as to allow some of the sweat on the skin to evaporate. Sweat-gland "fatigue" may involve other processes besides swelling of the stratum corneum, since prolonged sweating also causes histological changes, including depletion of glycogen, in the sweat glands.

THERMOREGULATORY RESPONSES DURING EXERCISE

CORE TEMPERATURE RISES DURING EXERCISE, TRIGGERING HEAT-LOSS RESPONSES.

Exercise increases heat production, causing an increase in core temperature, which in turn elicits heat-loss responses. Core temperature continues to rise, until heat loss has increased enough to match heat production and core temperature and the heat-loss responses reach new steady-state levels. Since the heat-loss responses are proportional to the increase in core temperature, the increase in core temperature at steady state is proportional to the rate of heat production, and thus to the metabolic rate.

A change in ambient temperature causes a change in the level of sweating and skin blood flow necessary to maintain any given level of heat dissipation; but the change in ambient temperature also elicits, via direct and reflex effects of the accompanying skin-temperature changes, a change of these responses in the right direction. For any given rate of heat production, there is a certain range of environmental conditions within which an ambient-temperature change elicits the necessary changes in heat-dissipating responses almost entirely through the effects of skin-temperature changes, with virtually no core-temperature change. (The limits of this range of environmental conditions depend on the rate of heat production, and such individual factors as skin surface area and state of heat acclimatization.) Within this range, the core temperature reached during exercise is nearly independent of ambient temperature; and for this reason it was once believed that the increase in core temperature during exercise is caused by an increase in the thermoregulatory set point,

just as during fever. As we have noted, however, the increase in core temperature with exercise is an example of a load error rather than an increase in set point. This difference between fever and exercise is shown in Fig. 12. Note these differences: First, although heat production may increase substantially (through shivering) when core temperature is rising early during fever, it does not need to stay high to maintain the fever, but in fact returns nearly to pre-febrile levels once the fever is established; during exercise, however, an increase in heat production not only causes the elevation in core temperature, but is necessary to sustain it. Second, while core temperature is rising during fever, rate of heat loss is, if anything, lower than it was before the fever began; but during exercise, the heat-dissipating responses and the rate of heat loss start to increase early and continue increasing as core temperature rises.

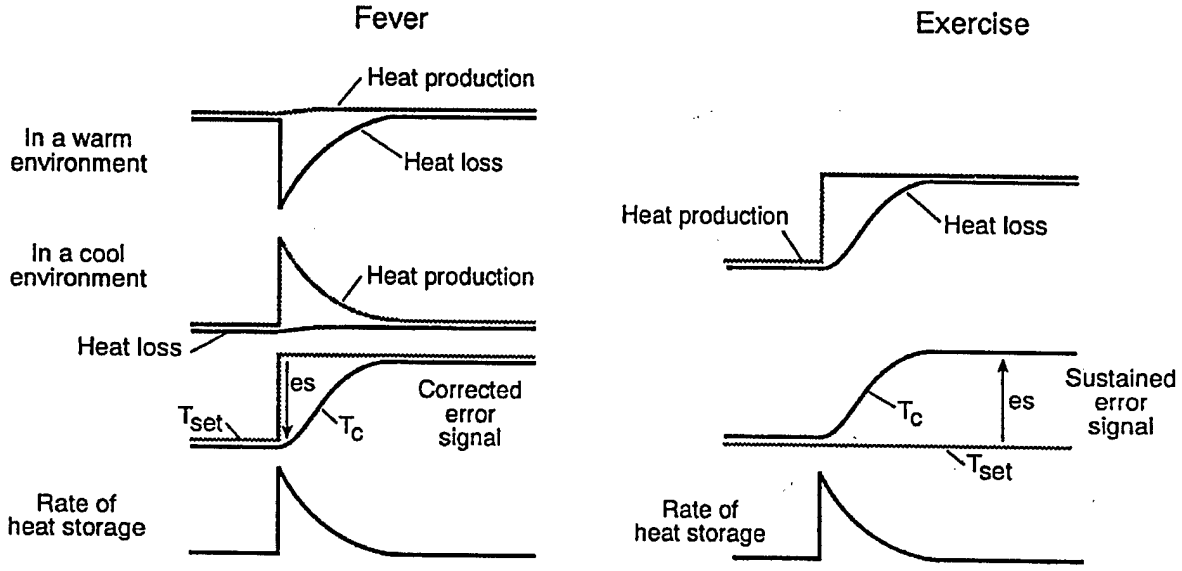

Figure 12. Thermal events during the development of fever (left) and the increase in core temperature during exercise (right). The error signal, es, is the difference between T_c and the set point, T_{set}. At the start of a fever, T_{set} has risen, so that T_{set} is higher than T_c and es is negative. At steady state, T_c has risen to equal the new level of T_{set} and es is corrected (i.e., it returns to zero.) At the start of exercise, $T_c = T_{set}$ so that es = 0. At steady state, T_{set} has not changed but T_c has increased and is greater than T_{set}, producing a sustained error signal, which is equal to the load error. [The error signal (or load error) is here represented with an arrow pointing downward for $T_c < T_{set}$, and with an arrow pointing upward for $T_c > T_{set}$.] (Modified from Stitt, J.T.. Fever versus hyperthermia. Fed. Proc. 38: 39-43, 1979.)

EXERCISE IN THE HEAT CAN THREATEN CARDIOVASCULAR HOMEOSTASIS.

The rise in core temperature during exercise increases the temperature difference between core and skin somewhat, but nowhere nearly enough to match the increase in metabolic heat production. Therefore as we saw earlier, skin blood flow must increase in order to carry all of the heat that is produced to the skin; and in a warm environment, where the temperature difference between core and skin is relatively small, the necessary increase in skin blood flow may be several liters per minute.

Impairment of cardiac filling during exercise in the heat

The work of providing the skin blood flow required for thermoregulation in the heat may impose a heavy burden on a diseased heart, but in healthy subjects the major cardiovascular burden of heat stress results from impairment of venous return. As skin blood flow increases, the dilated vascular bed of the skin becomes engorged with large volumes of blood, thus reducing central blood volume and cardiac filling (Fig. 13). Stroke volume is decreased, and a higher heart rate is required to maintain cardiac output. These effects are aggravated by a decrease in plasma volume if the large amounts of salt and water lost in the sweat are not replaced. Since the main cation in sweat is sodium, disproportionately much of the body water lost in sweat is at the expense of extracellular fluid, including plasma, although this effect is mitigated if the sweat is dilute.

Compensatory responses during exercise in the heat

Several reflex adjustments help to maintain cardiac filling, cardiac output, and arterial pressure during exercise and heat stress. The cutaneous veins constrict during exercise; and since most of the vascular volume is in the veins, constriction makes the cutaneous vascular bed less easily distensible, and reduces peripheral pooling. Splanchnic and renal blood flow diminish in proportion to the intensity of the exercise or heat stress. The reduction of blood flow has two effects. First, it allows a corresponding diversion of cardiac output to skin and exercising muscle. Second, since the splanchnic

vascular beds are very compliant, a decrease in their blood flow reduces the amount of blood pooled in them (Fig. 13), helping to compensate for decreases in central blood volume caused by reduced plasma volume and blood pooling in the skin. Because of the essential role of skin blood flow in thermoregulation during exercise and heat stress, the body preferentially compromises splanchnic and renal flow for the sake of cardiovascular homeostasis. Above a certain level of cardiovascular strain, however, skin blood flow too will be compromised.

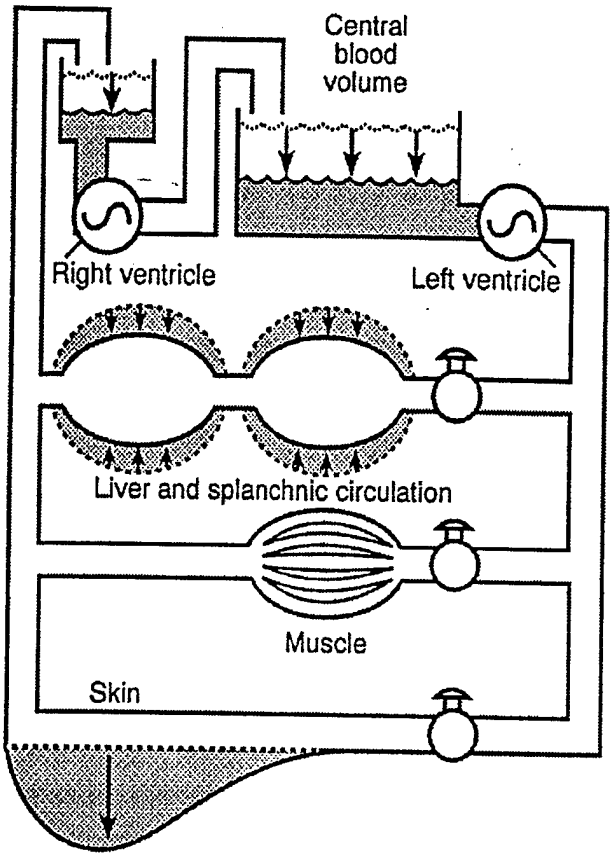

Figure 13. Schematic diagram of the effects of skin vasodilation on peripheral pooling of blood and the thoracic reservoirs from which the ventricles are filled, and also the effects of compensatory vasomotor adjustments in the splanchnic circulation. The valves drawn at the right sides of liver/splanchnic, muscle, and skin vascular beds represent the resistance vessels that control blood flow through those beds. Arrows show the direction of the changes during heat stress. (Redrawn from Rowell, L.B. Cardiovascular adjustments to thermal stress. In: Handbook of Physiology. Sect. 2. The Cardiovascular System. Vol. 3. Peripheral Circulation and Organ Blood Flow. J.T Shepherd and F. M. Abboud (Eds) Bethesda, MD: American Physiological Society, 967-1023, 1983, and Rowell, L. B. Cardiovascular aspects of human thermoregulation. Circ. Res. 52: 367-379, 1983.)

HEAT ACCLIMATIZATION

Prolonged or repeated exposure to stressful environmental conditions elicits significant physiological changes, called acclimatization, which reduce the physiological strain that such conditions produce. (Such changes are usually called by the nearly synonymous term acclimation when produced in a controlled experimental setting.) Some degree of heat acclimatization is produced either by heat exposure alone or by regular strenuous exercise, which raises core temperature and provokes heat-loss responses. Indeed, the first summer heat wave produces enough heat acclimatization that most people notice an improvement in their level of energy and general feeling of well being after a few days. However, the acclimatization response is greater if heat exposure and exercise are combined, so as to cause a greater rise of internal temperature and more profuse sweating. Evidence of acclimatization appears in the first few days of combined exercise and heat exposure, and most of the improvement in heat tolerance occurs within ten days. The effect of heat acclimatization on performance can be quite dramatic, so that acclimatized subjects can easily complete exercise in the heat which earlier was difficult or impossible.

HEAT ACCLIMATIZATION INCLUDES ADJUSTMENTS IN HEART RATE, TEMPERATURES, AND SWEAT RATE.

Cardiovascular adaptations that reduce the heart rate required to sustain a given level of activity in the heat appear quickly, and reach nearly their full development within a week. Changes in sweating develop more slowly. After acclimatization, sweating begins earlier and at a lower core temperature, i.e., the core-temperature threshold for sweating is reduced. The sweat glands become more sensitive to cholinergic stimulation, and a given elevation in core temperature elicits a higher sweat rate; and in addition the glands become resistant to hidromeiosis and fatigue, so that higher sweat rates can be sustained. These changes reduce the levels of core and skin temperatures reached during a given exercise-heat stress, increase the sweat rate, and enable one to exercise longer. The threshold for cutaneous vasodilation is reduced along with the threshold for sweating, so that heat transfer from core to skin is maintained.

The lower heart rate and core temperature and the higher sweat rate (Fig. 14) are the three classical signs of heat acclimatization. Other physiological changes also occur. During the first week, total body water and especially plasma volume increase. These changes likely contribute to the cardiovascular adaptations; but later the fluid changes seem to diminish or disappear though the cardiovascular adaptations persist. In an unacclimatized person, sweating occurs mostly on the chest and back; but during acclimatization—especially in humid heat—the fraction of sweat secreted on the limbs increases, to make better use of the skin surface for evaporation. An unacclimatized person who is sweating profusely can lose large amounts of sodium. With acclimatization, the sweat glands become able to conserve sodium by secreting sweat with a sodium concentration as low as 5 mEq/L. This effect is mediated through aldosterone, which is secreted in response to sodium depletion and also to exercise and heat exposure. The sweat glands respond to aldosterone more slowly than the kidneys, requiring several days; and unlike the kidneys, they do not escape from the

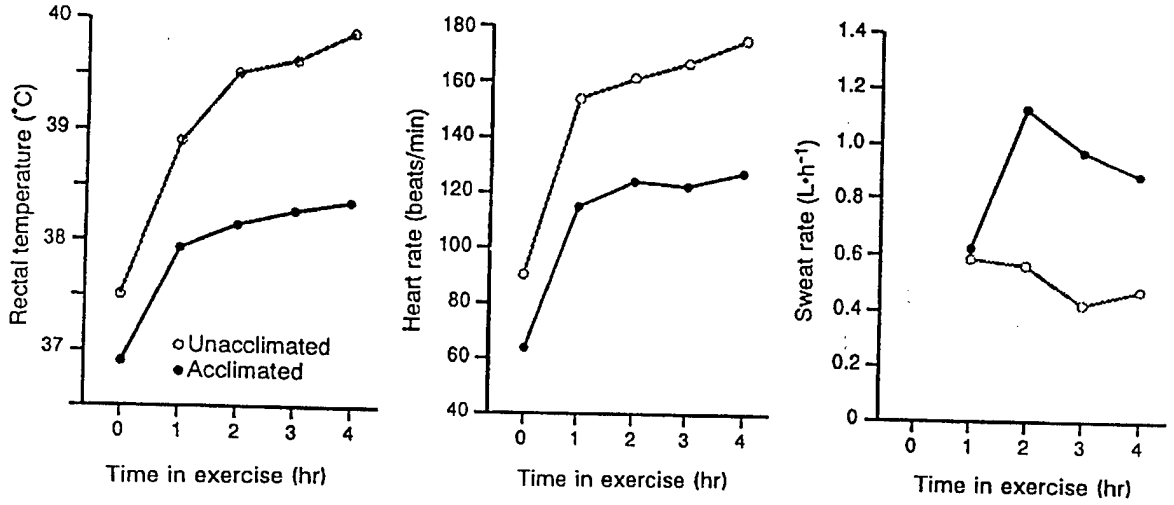

Figure 14. Rectal temperatures, heart rates, and sweat rates during 4 hours' exercise (bench stepping, 35W mechanical power) in humid heat (33.9°C dry bulb, 89% relative humidity, 35mmHg ambient vapor pressure) on the first and last days of a two-week program of acclimation to humid heat. (Modified from Wenger, C.B. Human heat acclimatization. In: Human Performance Physiology and Environmental Medicine at Terrestrial Extremes (Chap. 4) K.B. Pandolf, M.N. Sawka, and R.R. Gonzalez (Eds.) Indianapolis: Benchmark, 153-197, 1988.)

influence of aldosterone once sodium balance has been restored, but continue to conserve sodium as long as acclimatization persists.

Heat acclimatization is transient, and disappears in a few weeks if not maintained by repeated heat exposure. The components of heat acclimatization are lost in the order in which they were acquired, so that the cardiovascular changes decay more quickly than the reduction in exercise core temperature and the sweating changes.

RESPONSES TO COLD

The body maintains core temperature in the cold by minimizing heat loss, and, when this is not sufficient, by increasing heat production. Reducing core-to-skin thermal conductance is the chief physiological means of heat conservation in humans. Furred or hairy animals also can increase the thickness of their coat, and thus its insulating properties, by making the hairs stand on end. This response, called piloerection, makes a negligible contribution to heat conservation in humans, but manifests itself as "goose flesh".

BLOOD VESSELS IN THE SHELL CONSTRICT TO CONSERVE HEAT.

Constriction of cutaneous arterioles reduces skin blood flow and core-to-skin thermal conductance. Constriction of the superficial limb veins further improves heat conservation by diverting venous blood to the deep limb veins, which lie close to the major arteries of the limbs and do not constrict in the cold. (Many penetrating veins connect the superficial veins to the deep veins, so that venous blood from anywhere in the limb potentially can return to the heart via either superficial or deep veins.) In the deep veins, cool venous blood returning to the core can take up heat from the warm blood in the adjacent deep limb arteries. Thus some of the heat contained in the arterial blood as it enters the limbs takes a "short circuit" back to the core; and when the arterial blood reaches the skin it is already cooler than the core, and so loses less heat to the skin than it otherwise would. (When the superficial veins dilate in the heat, most venous blood returns via superficial veins so as to maximize core-to-skin heat flow.) The

transfer of heat from arteries to veins by this "short circuit" is called countercurrent heat exchange; and it can cool the blood in the radial artery of a cool but comfortable subject to as low as 30°C by the time it reaches the wrist.

As we saw earlier, the shell's insulating properties increase in the cold, as its blood vessels constrict and its thickness increases. Furthermore, the shell includes a fair amount of skeletal muscle in the cold; and although muscle blood flow is not believed to be affected by thermoregulatory reflexes, it is reduced by direct cooling. In a cool subject, the resulting reduction in muscle blood flow adds to the shell's insulating properties. As the blood vessels in the shell constrict, blood is shifted to the central blood reservoir in the thorax. This shift produces many of the same effects as an increase in blood volume, including diuresis (so-called cold diuresis) as the kidneys respond to the increased central blood volume.

Once skin blood flow is near minimal, metabolic heat production increases. In human adults, nearly all of this increase occurs in skeletal muscles, as a result first of increased tone, and later of frank shivering. Shivering may increase metabolism at rest by more than four fold acutely, but only about half that amount can be sustained after several hours.

HUMAN COLD ACCLIMATIZATION CONFERS A MODEST ADVANTAGE.

The pattern of human cold acclimatization depends on the nature of the cold exposure. It is partly for this reason that the occurrence of cold acclimatization in humans was long controversial. Our knowledge of human cold acclimatization comes both from laboratory studies and from studies of populations whose occupation or way of life exposes them repeatedly to cold.

Metabolic changes in cold acclimatization

At one time it was believed that humans must acclimatize to cold as laboratory mammals do, by increasing their metabolic rate. There are a few reports of increased basal metabolic rate, and sometimes also thyroid activity, in winter; and there is

evidence for functioning brown fat in the neck and mediastinum of outdoor workers. More often, however, increased metabolic rate has not been observed in studies of human cold acclimatization. In fact, there are a number of reports of the opposite response, consisting of a lower core temperature threshold for shivering, with a greater fall in core temperature and a smaller metabolic response during cold exposure. Such a response would spare metabolic energy, and so might be advantageous in an environment that is not so cold that a blunted metabolic response would allow core temperature to fall to dangerous levels.

Increased tissue insulation in cold acclimatization

A lower core-to-skin conductance (i.e., increased insulation by the shell) has often been reported in studies of cold acclimatization in which a reduction in the metabolic response to cold occurred. This increased insulation is not due to subcutaneous fat (in fact, it has been observed in very lean subjects), but apparently results from lower blood flow in the limbs or improved countercurrent heat exchange in the acclimatized subjects. In general, the cold stresses that elicit a lower core-to-skin conductance after acclimatization involve either cold-water immersion or exposure to air temperatures that are chilly but not so cold as to risk freezing the vasoconstricted extremities.

Cold-induced vasodilation and the Lewis hunting response

As the skin is cooled below about 15°C, its blood flow begins to increase somewhat, a response called cold-induced vasodilation (CIVD). CIVD is elicited most easily in comfortably warm subjects and in skin rich in arteriovenous anastomoses, i.e. in the hands and feet. The mechanism has not been established, but may involve a direct inhibitory effect of cold on contraction of vascular smooth muscle or on neuromuscular transmission. After repeated cold exposure, CIVD begins earlier during cold exposure, produces higher levels of blood flow, and takes on a rhythmical pattern of alternating vasodilation and vasoconstriction. This is called the Lewis hunting response, since the rhythmic pattern of blood flow is supposed to suggest that it is "hunting" for its proper level. This response is often well developed in workers whose

hands are exposed to cold, such as fishermen working with nets in cold water. Since the Lewis hunting response increases heat loss from the body somewhat, it is debatable whether it is truly an example of acclimatization to cold. It is, however, advantageous since it keeps the extremities warmer and more comfortable and functional, and probably protects them from cold injury.

CLINICAL ASPECTS OF THERMOREGULATION

Temperature is important clinically because of the presence of fever in many diseases; the effects of many factors on tolerance to heat or cold stress; and the effects of heat or cold stress in causing or aggravating certain disorders.

FEVER ENHANCES DEFENSE MECHANISMS.

Infection, inflammatory processes such as collagen-vascular diseases, trauma, neoplasms, acute hemolysis, and diseases due to immune mechanisms release an assortment of proteins, protein fragments, and bacterial lipopolysaccharide toxins, which collectively are called pyrogens or exogenous pyrogens. Exogenous pyrogens stimulate monocytes and macrophages to release endogenous pyrogen (EP), a protein which causes the thermoreceptors in the hypothalamus (and perhaps elsewhere in the brain) to alter their firing rate and input into the thermoregulatory integrating centers, and thereby raises the thermoregulatory set point. This effect of EP is believed to be mediated by local release of prostaglandins. Aspirin and other drugs which inhibit the synthesis of prostaglandins also reduce fever.

Fever accompanies disease so frequently, and is such a reliable indicator of the presence of disease, that body temperature is probably the most commonly measured clinical index. Many of the body's defenses against infection and cancer are elicited by a group of proteins called cytokines, and EP is now identified with a member of this group, interleukin 1 (IL-1). (However other cytokines, particularly tumor necrosis factor and interleukin-6 are pyrogenic too.) Recent evidence indicates that elevated body temperature enhances the development of these defenses, contradicting the long-held belief that fever confers no benefit. (Although in this report fever means specifically an

elevation in core temperature due to pyrogens, the reader should be aware that some authors use fever more generally to mean any significant elevation of core temperature.)

MANY FACTORS, INCLUDING PHYSICAL FITNESS, AGE, DRUGS, AND DISEASES, AFFECT THERMOREGULATORY RESPONSES AND TOLERANCE TO HEAT AND COLD.

Regular physical exercise and heat acclimatization increase heat tolerance and the sensitivity of the sweating response. Ageing has the opposite effect, and in healthy 65-year-old men the sensitivity of the sweating response is half that in 25-year-old men. Many drugs inhibit sweating, most obviously those used for their anticholinergic effects, such as atropine and scopolamine. In addition, some drugs used for other purposes, such as glutethimide (a sleep medicine), tricyclic antidepressants, phenothiazines (tranquilizers and antipsychotic drugs), and antihistamines also have some anticholinergic action; and all of these, plus several others, have been associated with heat stroke. Neurological diseases that involve the thermoregulatory structures in the brainstem can impair thermoregulation. Although such disorders can produce hypothermia (abnormally low core temperature), hyperthermia (abnormally high core temperature) is more usual, and typically is characterized by loss of sweating and the circadian rhythm. Congestive heart failure and certain skin diseases impair sweating, and in patients with these diseases, heat exposure and especially exercise in the heat may raise body temperature to dangerous levels. Ichthyosis and anhidrotic ectodermal dysplasia are often cited as examples of skin disorders that impair sweating, and they may have a profound effect on thermoregulation in the heat. In addition, heat rash (miliaria rubra) and even mild degrees of sunburn impair sweating and may reduce tolerance to exercise in the heat. Sunburn also impairs vasoconstriction during cold exposure. The thermoregulatory effects of heat rash and sunburn may persist for a time after the appearance of the skin has returned to normal.

Certain drugs, such as barbiturates, alcohol, and phenothiazines; and certain diseases, such as hypothyroidism, hypopituitarism, congestive heart failure, and septicemia, may impair the defenses against cold. (Thus septicemia, especially in

debilitated patients, may be accompanied by hypothermia, instead of the usual febrile response to infection.) Furthermore newborn infants and many healthy elderly persons are less able than older children and younger adults to maintain body temperature in the cold. This appears to be due to a reduced ability both to conserve body heat by reducing heat loss, and to increase metabolic heat production in the cold.

HEAT STRESS CAUSES OR AGGRAVATES A NUMBER OF DISORDERS.

The harmful effects of heat stress are exerted through cardiovascular strain, fluid and electrolyte loss, and—especially in heat stroke—tissue injury whose mechanism is uncertain. In a patient suspected of having hyperthermia secondary to heat stress, temperature should be measured in the rectum, since hyperventilation may render oral temperature spuriously low.

Heat syncope

Heat syncope is circulatory failure due to pooling of blood in the peripheral veins with a consequent decrease in venous return and diastolic filling of the heart and thus in cardiac output, and a fall of arterial pressure. Symptoms range from lightheadedness and giddiness to loss of consciousness. Thermoregulatory responses are intact, so that core temperature typically is not substantially elevated, and the skin is wet and cool. The large thermoregulatory increase in skin blood flow in the heat is probably the primary cause of the peripheral pooling. Heat syncope affects mostly those who are not acclimatized to heat.

Water and salt depletion due to heat exposure

Water and salt can be lost rapidly in the sweat, and people exercising in the heat drink less water than they are losing if they drink only according to their feelings of thirst. Therefore complete water replacement during heat stress is difficult even if ample water is available, and gradual progressive dehydration is likely to occur. Salt loss in the sweat is quite variable, and some people lose enough salt to become salt depleted even though water is replaced. Thus heat exhaustion may be associated either

predominantly with salt depletion or predominantly with water depletion. Since body water is distributed so as to maintain osmotic balance between the intra- and extracellular spaces, the body water of salt-depleted patients is lost predominantly from the extracellular space, so that these patients are hypovolemic out of proportion to the degree of dehydration.

Like heat syncope, heat exhaustion is characterized by reduced diastolic filling of the heart; but hypovolemia plays a much greater role in its development, and the baroreflex responses are usually sufficient to maintain consciousness in spite of the hypovolemia. The baroreflex responses may be manifested in nausea, vomiting, pallor, cool or even clammy skin, and tachycardia. The patient usually is sweating profusely. Heat exhaustion ranges from fairly mild disorders which respond well to rest in a cool environment and oral fluid replacement, to severe forms which require intravenous replacement of fluid and salt and may be accompanied by collapse, confusion, and hyperthermia. Unconsciousness is infrequent, but there may be vertigo, ataxia, headache, weakness, and low blood pressure. Dehydration impairs thermoregulation, and heat exhaustion may lead to heat stroke. Therefore patients should be actively cooled if rectal temperature is 40.6°C (105°F) or higher.

Heat stroke

The most severe and dangerous heat disorder is characterized by rapid development of hyperthermia and severe neurological disturbances, with loss of consciousness and, frequently, convulsions. Hepatic and renal injury and disturbances of blood clotting are frequent accompaniments. The pathogenesis is not well understood. Factors besides hyperthermia probably contribute to its development, and several lines of evidence suggest that products of the bacterial flora in the gut—perhaps lipopolysaccharide endotoxins—enter the circulation and play an important role in the development of heat stroke.

Heat stroke occurs in two forms, classical and exertional. In the classical form, the primary factor is environmental heat stress which overwhelms an impaired thermoregulatory system, whereas in exertional heat stroke the primary factor is high

metabolic heat production. Patients with exertional heat stroke tend to be younger and physically fitter (typically, soldiers and athletes) than patients with the classical form. The traditional diagnostic criteria of heat stroke—coma, hot dry skin, and rectal temperature above 41.3°C (106°F)—are seen primarily with the classical form. Patients with exertional heat stroke tend to have somewhat lower rectal temperatures, and may be sweating profusely. Heat stroke is a medical emergency, with a high mortality if not treated promptly and vigorously. Prompt lowering of core temperature is the cornerstone of treatment, and is most effectively accomplished by immersion in cold water.

Malignant hyperpyrexia, or malignant hyperthermia, a rare process triggered by inhalational anesthetics or neuromuscular blocking agents, was once considered a form of heat stroke, but is now known to be a distinct disorder that occurs in genetically susceptible individuals. Susceptibility may be associated with any of several myopathies, or may occur as an autosomal dominant trait without other clinical manifestations. In 90% of susceptible individuals, biopsied skeletal muscle tissue contracts on exposure to caffeine, halothane, or hexamethonium, in concentrations having little effect on normal muscle. Re-uptake of calcium ion by the sarcoplasmic reticulum is severely impaired so that calcium concentration in the cytoplasm rises, activating myosin ATP-ase and leading to an uncontrolled hypermetabolic process which produces a rapid rise in core temperature. Dantrolene sodium, which appears to act by reducing release of calcium ion from the sarcoplasmic reticulum, is a specific treatment and has dramatically reduced the mortality rate of this disorder.

Aggravation of disease states due to heat exposure

Besides producing specific disorders, heat exposure aggravates a number of other diseases. Epidemiological studies show that during unusually hot weather, mortality may be two to three times that normally expected for the months in which the "heat waves" occur. Deaths ascribed to specific heat disorders account for only a small fraction of the excess mortality, i.e., the increase above the mortality expected for the month. Most of the excess mortality is accounted for by deaths from diabetes, various diseases of the cardiovascular system, and diseases of the blood-forming organs.

HYPOTHERMIA OCCURS WHEN THE BODY'S DEFENSES AGAINST COLD ARE DISABLED OR OVERWHELMED.

Hypothermia reduces metabolic rate via the Q_{10} effect, and thus prolongs the time that tissues can safely tolerate loss of blood flow. Since the brain is damaged by ischemia soon after circulatory arrest, controlled hypothermia is often used to protect the brain during surgical procedures in which its circulation is occluded or the heart is stopped. Much of our knowledge about the physiological effects of hypothermia comes from observations on surgical patients.

During the initial phases of cooling, stimulation of shivering through thermoregulatory reflexes overwhelms the Q_{10} effect. Therefore metabolic rate increases, reaching a peak at a core temperature of 30-33°C. At lower core temperatures, however, metabolic rate is dominated by the Q_{10} effect, and thermoregulation is lost. A "vicious circle" develops, wherein a fall in core temperature depresses metabolism, and allows core temperature to fall further, so that at 17°C, O_2 consumption is about 15%, and cardiac output 10%, of precooling values.

Hypothermia that is not induced for therapeutic purposes is called accidental hypothermia. Accidental hypothermia occurs in individuals whose defenses are impaired by drugs (especially ethanol, in the U.S.A.) or by disease or other physical condition; and in healthy individuals who are immersed in cold water or become exhausted working or playing in the cold. Hypothermia is classified according to the patient's core temperature as mild (32-35°C), moderate (28-32°C), or severe (below 28°C). Shivering is usually prominent in mild hypothermia, but diminishes in moderate hypothermia, and is absent in severe hypothermia. The pathophysiology is characterized chiefly by the depressant effect of cold (via the Q_{10} effect) on multiple physiological processes, and differences in the degree of depression of each process. Apart from shivering, the most prominent features of mild and moderate hypothermia are due to depression of the central nervous system. These begin with mood changes (commonly apathy, withdrawal, and irritability) progressing, as hypothermia deepens, to confusion and lethargy, and ataxia and speech and gait disturbances, which may mimic a cerebrovascular accident ("stroke"). In severe hypothermia, voluntary movement,

reflexes, and consciousness are lost, and muscular rigidity appears. Cardiac output and respiration decrease as core temperature falls. Myocardial irritability increases in severe hypothermia, causing a substantial danger of ventricular fibrillation, with the risk increasing as cardiac temperature falls. The primary mechanism presumably is that cold depresses conduction velocity in Purkinje fibers more than in ventricular muscle, favoring the development of circus-movement propagation of action potentials; but myocardial hypoxia also contributes. In more profound hypothermia, cardiac sounds become inaudible, and pulse and blood pressure are unobtainable, because of circulatory depression; the electrical activity of the heart and brain becomes unmeasurable; and extensive muscular rigidity may mimic rigor mortis. The patient may appear clinically dead, but patients have been revived from core temperatures as low as 17°C, so that "no one is dead until warm and dead". The usual causes of death during hypothermia are cessation of respiration and failure of cardiac pumping, because of either ventricular fibrillation or direct depression of cardiac contraction.

Depression of renal tubular metabolism by cold impairs reabsorption of sodium, causing a diuresis and leading to dehydration and hypovolemia. Acid-base disturbances in hypothermia are complex. Respiration and cardiac output typically are depressed more than metabolic rate, and a mixed respiratory and metabolic acidosis results, due to CO_2 retention and lactic acid accumulation, and also to the cold-induced shift of the hemoglobin-O_2 dissociation curve to the left. Acidosis aggravates the susceptibility to ventricular fibrillation.

Treatment consists of preventing further cooling, and restoring fluid, acid-base, and electrolyte balance. Patients in mild to moderate hypothermia may be warmed solely by providing abundant insulation to promote retention of metabolically produced heat; but those who are more severely affected require active rewarming. The most serious complication associated with treating hypothermia is development of ventricular fibrillation. Vigorous handling of the patient may trigger this, but an increase in the patient's circulation (associated, e.g., with warming or skeletal muscle activity) may itself increase the susceptibility to such an occurrence. This may happen as follows: peripheral tissues of a hypothermic patient are, in general, even cooler than the core, including the heart; and acid products of anaerobic metabolism will have accumulated

in underperfused tissues while the circulation was most depressed. As the circulation increases, a large increase in blood flow through cold, acidotic peripheral tissue may return enough cold, acidotic blood to the heart to cause a transient drop in the temperature and pH of the heart, and increase its susceptibility to ventricular fibrillation.

The diagnosis of hypothermia is usually straightforward in a patient rescued from the cold, but may be far less clear in a patient in whom hypothermia is the result of a serious impairment of physiological and behavioral defenses against cold. A typical example is the elderly person, living alone, who is discovered at home, cool and obtunded or unconscious. The setting may not particularly suggest hypothermia, and when the patient comes to medical attention, the diagnosis may easily be missed, since standard clinical thermometers are not graduated low enough (usually only to 34.4°C) to detect hypothermia, and in any case do not register temperatures below the level to which the mercury has been shaken. Because of the depressant effect of hypothermia on the brain, the patient's condition may be misdiagnosed as cerebrovascular accident or other primary neurological disease. Recognition of this condition thus depends on the physician's considering it when examining a cool, obtunded patient, and obtaining a true core temperature with a low-reading glass thermometer or other device.

Table 3. Illustrative values for thermal physiology

Measurement	S.I*. Units	Traditional Heat Units
Energy equivalent of oxygen for a mixed diet	20.2kJ/L	4.83kcal/L
heat of evaporation of water	2.43kJ/g	0.58kcal/g
data for a "typical" healthy lean young man		
mass	70kg	
body surface area	$1.8m^2$	
mean specific heat of the body	3.55kJ/(kg·°C)	0.85kcal/(kg·°C)
volume specific heat of blood	3.85kJ/(L·°C)	0.92kcal/(L·°C)
maximum rate of O_2 consumption	3.5L/min	
metabolic rate at rest**	$45W/m^2$	$52.3kcal/(m^2 \cdot h)$
core-to-skin conductance** with minimal skin blood flow	$9W/(m^2 \cdot °C)$	$10.5kcal/(m^2 \cdot °C \cdot h)$

* Système Internationale (in which heat is expressed in units of work)
** per m^2 of body surface area

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